Henry Ford Hospital Medical Bulletin

Vol. 7 December, 1959 No. 4

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HENRY FORD HOSPITAL MEDICAL BULLETIN

Published quarterly by the Professional Staff of the
Henry Ford Hospital and The Edsel B. Ford Institute for Medical Research

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Vol. 7 December 1959 No. 4

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Henry Ford Hospital
1959

EDITORIAL
PULMONARY FINDINGS IN THE COLLAGEN DISEASES*

WILLIAM R. EYLER, M.D.

A number of systemic diseases which have been classed together in spite of considerable diversity of manifestations were first called "diffuse collagen disease" by Klemperer and his co-workers in 1942. They applied this term to disseminated lupus erythematosus, scleroderma, and dermatomyositis. Since then rheumatoid arthritis, acute rheumatic fever, periarteritis nodosa, and thrombotic thrombocytopenic purpura have been added. Hamman-Rich syndrome, Whipple's disease, and hypersensitivity angiitis are not included, though it has been suggested that they should be.

This group of diseases involves soft parts generally and blood vessels specifically in many instances. Some mechanisms have been discovered. In the case of lupus erythematosus there is little question about the presence of abnormal proteins in the blood, disturbance of desoxyribosenucleic acid metabolism of the mesenchyme, and the L. E. cell phenomenon. In all of the group, except possibly scleroderma, there must be consideration of hypersensitivity as a pathogenetic factor.

The relationship of the histopathologic changes in these diseases is emphasized by the occurrence of findings characteristic of more than one of the disorders in a single patient; the clinical overlapping of symptom complexes is considerable. Five per cent of patients with scleroderma, for example, show glomerular lesions similar to those of lupus erythematosus. Geschickter and others[8] report that the application of a simple irritant amine to experimental animals is capable of causing the histopathologic changes of all of the more common collagen diseases. In this experimental work, the animals presumably respond in these several fashions to a single injurious substance, which, however, may have many sites of action. Other forms of trauma, even as simple as pinching the skin, can cause the fibrinoid necrosis typical of the group.

The acute manifestations of disseminated lupus erythematosus which may appear on films of the chest include pleural effusions of any size, either unilateral or bilateral, pulmonary edema, and pneumonitis of several types with some predilection for localization in the subpleural areas (Thorell,[17]). Patients in this group are also more prone than the general population to ordinary bacterial pneumonias. These probably follow pulmonary edema. Sante and Wyatt[15] have pointed out that edema, congestion, and hemorrhage occur in the lungs when the collagen disease involves the kidneys — the so-called "antigenic (azotemic) pneumonitis." Purnell, Baggenstoss, and Olsen[12] described basophilic mucinous edema, interstitial pneumonitis, and alveolar hemorrhage in some of their cases. The acute pulmonary edema of lupus erythematosus is not always associated with severe cardiac or renal lesions; in this event the edema may be due to the direct action of the disease in the lungs or to protein disturbances. The pulmonary abnormalities in lupus may change quite rapidly. Fibrosis may follow acute lesions or appear without known preceding involvement; it produces a fine linear and nodular pattern, narrowed vessels, and at times cor pulmonale. This may progress to a reticular or fine cystic appearance.

Periarteritis nodosa may also show "antigenic (azotemic) pneumonitis" on the

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basis of involvement of the general body economy secondary to renal lesions. In addition, changes can result from a specific local vascular lesion in the pulmonary or bronchial arteries or both (Doub[6] *et al.*, Braunstein,[1]). When there is a localized arterial lesion, pulmonary infarction, frequently resulting in cavitation, may be seen. Changing patches of pulmonary edema and hemorrhage are present and may be followed by a linear and fibrotic pattern as in lupus erythematosus. Enlargement of the lung roots is a common roentgen observation. The localized vascular lesions of periarteritis may also cause widespread arterial destruction throughout the lungs. Death usually ensues in a short time. Many lesions of Wegener's granulomatosis may for all practical purposes be considered a localized periarteritis causing an infarct; others are "granulomas" with necrotic centers.

Although in some cases of scleroderma there is a diffuse and patchy infiltrative process in the lungs, indistinguishable from the changes seen in other members of this group of diseases, there is also a typical "sclerocystic" appearance with a very fine honeycomb pattern which is thought to be characteristic. This is the result of coalescence of alveoli and formation of "broncho-alveolar cysts." There is associated marked interstitial fibrous thickening following subepithelial myxomatous change. In some of our material there has been a severe bronchiectasis in the lower lobes.

The nature of the transient densities appearing in the lungs in acute rheumatic fever is not established. Some are probably the result of congestive failure, incomplete infarction, and hemorrhage. However, a highly fatal type of pneumonia has been found in a number of autopsy studies of patients who have had extensive hyaline membrane formation, Masson bodies, and mononuclear cell infiltrates[9,11,15]. The roentgen appearance in these cases has varied from diffuse mottling to homogeneous consolidation of large portions of both lungs.

Much has been written recently concerning the pulmonary lesions in patients with rheumatoid arthritis. Ellman and Ball[7] and Christie[5] reported complete autopsy study of cases of rheumatoid arthritis with pleural lesions and with lesions in the parenchyma, vessels, bronchi, and lymph nodes of the lungs. These lesions were in all stages of development and of varying degrees of severity. Small foci of necrotizing pneumonia with fibrinoid changes were followed by the development of collagenous tissue. Small necrotic nodules were formed from fibrinous pneumonia, and in one case there was progression to the formation of a massive rheumatoid nodule, 7 cm. in diameter. Fibrotic nodules and strands as well as fibrosis of vessels and bronchi were found. Gresham and Kellaway[10] published a case of rheumatoid arthritis showing cystic changes in the subpleural areas, with reproduction of sections containing both the cystic changes and active rheumatoid nodules. They were unable to establish the origin of the cysts from the granulomatous destruction of lung. Histochemical observations of the lung lesions were similar to those of a juxta-articular rheumatoid nodule. The patient also had cardiac lesions with aortic incompetence, thickening of cusp margins, and fusion of the commissures. The valve showed fibrinoid necrosis bordered by palisading histiocytes. Similar cystic and granulomatous lesions are present in our material[16]. Fine fibrotic lesions like the Hamman-Rich syndrome are reported by Read[13].

Coal miners with rheumatoid disease have been found by Caplan[3] to have lung lesions of a particular type, somewhat resembling massive fibrosis, but more numerous, round, and more uniformly distributed through the lungs. These lesions were observed in the presence of slight or no generalized radiographic changes of pneumoconiosis. They developed rapidly and then could remain unchanged or appear in successive waves. Sometimes they disappeared or became fibrotic after cavitation. Some calcified or became incorporated in progressive massive fibrosis. Caplan and others[4] have described this process in a foundry worker, and it has been seen in pottery workers, sand blasters, boiler scalers[2], and brass and iron foundry workers. Microscopically the border of the lesion shows a rheumatoid type of inflammation with formation of collagen and variable amounts of necrosis.

Typical foci of rheumatoid nodules localized mainly to the subpleural portions of the lower lungs are described in association with asbestosis by Rickards and Barrett[14]. They recognized 26 cases of necrobiotic foci of typical rheumatoid lesions and stated that 15 of them were associated with pneumoconiosis. These cases show the altered response of a patient with a particular collagen disease to a given type of injury.

Pulmonary lesions are frequent in lupus erythematosus, periarteritis nodosa, and scleroderma, but infrequent in rheumatic fever, rheumatoid arthritis, and dermatomyositis.

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THE IMPORTANCE OF COMPLETE ANGIOGRAPHY IN CEREBROVASCULAR INSUFFICIENCY SYNDROME*

ROBERT S. KNIGHTON, M.D., AND SALVADOR GONZALEZ, M.D.**

Atherosclerotic disease of the carotid vessels in the neck is being diagnosed with greater frequency since Sjöqvist (1936)[1] and Moniz (1947)[2] first reported on the angiographic findings in such cases. Neurosurgeons are finding carotid occlusion or segmental partial occlusion with increasing frequency as a result of more frequent and more complete angiographic studies of patients having symptoms and signs of cerebrovascular disease. More complete pathological studies at autopsy are confirming the presence of atherosclerotic or narrowings in the neck vessels and clarifying the clinical syndrome produced. Physicians are now aware that this disease has many neurological manifestations from vague transitory sensory symptoms, primarily in the face and hand, to profound permanent hemiplegia.

Gowers (1875)[3], Guthrie and Mayou (1908)[4] recorded cases of unilateral blindness associated with contralateral hemiplegia. Hunt (1914)[5] described the role of the carotid arteries in the causation of vascular lesions of the brain and stressed the importance of palpation of the carotid artery in the neck as a means of diagnosing disease of the carotid artery. Fisher (1951)[6] pointed out the frequency of carotid artery occlusion as a causation of cerebrovascular accident and raised the question of surgical therapy for this condition. Johnson and Walker (1951)[7] reviewed the literature and found 101 angiographically proven cases of thrombosis of the carotid artery and reported six cases of their own.

Diagnosis of internal carotid artery occlusion or stenosis cannot be made with absolute certainty on purely clinical evaluation. However, the following signs, or maneuvers, together with an accurate history of intermittent episodes, makes the diagnosis reasonably tenable.

PALPATION OF THE CAROTID ARTERY in the neck may reveal a complete absence of the pulse or decreased pulsation in the entire vessel on one side of the neck. However, palpation of the internal carotid artery at the bifurcation, or in the tonsillar fossa, is unreliable because it is not possible to separate the pulses of the internal and external carotid arteries.[8,9] In addition, a good pulse may be felt in the presence of internal carotid thrombosis due to the thrust of the common carotid artery with each pulsation.

With atherosclerotic disease at the bifurcation, a SYSTOLIC BRUIT may often be heard on auscultation. Frequently this is due to a segmental stenosis or actual occlusion of the internal carotid artery but it can also be due to diffuse disease with increased tortuosity and roughening of the vessel walls.

Recently the use of OPHTHALMODYNAMOMETRY[10,11] to measure the blood pressure of the retinal arteries, has been shown to be helpful. In cases of complete or partial occlusion of the carotid artery the retinal artery pressure on the involved

*Presented at the 5th Western Medical Assembly
University of Guadalajara, Mexico — Nov. 10-14, 1959.
**Division of Neurological Surgery.

side is usually lowered to approximately one-third or one-half of the pressure in the opposite eye. This procedure, while useful, is subject to some error of interpretation.

Another maneuver of considerable importance has recently been popularized by Gurdjian and Webster. [12,13,14] This consists of COMPRESSION OF THE COMMON CAROTOID ARTERIES below the bifurcations. In the presence of thrombosis of the anterior cerebral artery or the internal carotid artery on the contralateral side, or of the vertebral basilar system, syncope or convulsions may occur within 15 to 20 seconds. Compression in the presence of occlusion of the middle cerebral artery usually does not cause syncope. Compression is made well below the bifurcation to avoid the syncope associated with hypersensitivity of the carotid sinus. Slow wave changes in the electoencephalogram usually coincide with the onset of syncope.

At present, the exact incidence of carotid occlusion and stenosis is not known with certainty. Fisher's excellent work on this subject leaves little doubt that it is one of the common causes of cerebrovascular accidents. In 432 routine, unselected autopsies in adults, Fisher[6,15] found occlusion or severe stenosis of one or both internal carotid arteries at the bifurcation in the neck in approximately ten percent of cases. Furthermore, a clinical pathological study of 45 cases of occlusion of the internal carotid artery at the bifurcation revealed that in 85 percent severe neurological disturbances were produced. Lofstrom, Webster and Gurdjian[16] found internal carotid artery occlusion or stenosis to be present in 29 of 100 consecutive cases of hemiparesis or hemiplegia.

More recently, studies by Crawford, DeBakey and Fields,[17], using percutaneous subclavian angiography, have shown that stenosing lesions may also be present at the origins of the carotid and vertebral vessels.

In our own experience this is by far less common than stenosis at the bifurcation in the neck and also is more difficult to correlate with the patient's clinical picture. In fifty consecutive subclavian arteriograms, we have found only three lesions at the origin of the vertebral artery which can be considered as having surgical significance. The remainder have shown no abnormality or diffuse sclerosis with no localized stenosis at the origin of the vessels. (FIG. 1).

In spite of all the clinical methods available for diagnosing vascular lesions in the major vessels leading to the brain, accurate diagnosis as to degree and site of occlusion cannot be made without complete angiographic studies. Indeed, symptomatology suggestive of vascular insufficiency due to occlusive disease, may occasionally be very misleading and if not verified by angiography result in improper treatment. We have personally had experience with cases of brain tumor, brain abscess, and subdural hematoma which clinically simulated episodes of vascular insufficiency as manifested by intermittent episodes of hemaparesis or other neurologic symptoms or signs. Since the use of anticoagulant medication is a popular method of treating the symptoms presumed to be due to vascular insufficiency, it is doubly important that this diagnosis be established by complete angiographic studies so that treatment may be carried out in a more intelligent manner. For instance, a short segmental stenosis of the internal carotid artery with essentially normal appearing distal branches of this vessel is best

Figure 1

Subclavian arteriogram showing stenosing lesion at the origin of the right vertebral artery as well as stenosis of the internal carotid artery above the bifurcation.

treated by endarterectomy, whereas a more diffusely involved vessel producing the same symptomatology might better be suited to anticoagulant therapy.

At present, it is our opinion that with some exceptions, patients who have had a cerebrovascular accident, or symptoms suggesting cerebrovascular insufficiency, should have arteriographic studies as soon as the patient's condition will tolerate the procedure. Obvious contraindications would be those patients in preterminal state with massive cerebral hemorrhage or infarctions. Age and general health particularly cardiac status, diabetes, etc., are also factors to be considered. The intracranial circulation, the bifurcation of the carotid arteries in the neck, and the origins of the carotid and vertebral vessels, are studied by various combinations of aortic, subclavian and carotid arteriography. Stenosing or occlusive disease is found to be far more common

at the carotid bifurcations than it is at the origins of these vessels and is said to be more common than in any other vessel except the abdominal aorta.[18]

While there is certainly some risk to complete angiographic study, its relative safety is demonstrated by the accompanying table showing the complications occurring

Complications following arteriography in 1822 injections in 540 patients.

Case	Age	Diagnosis	Arteriogram	Complication
1	56	Metastatic brain tumor	Carotid	Became less responsive temporarily following procedure.
2	41	Metastatic brain tumor	Carotid	Generalized seizures.
3	48	Parasellar meningioma	Carotid	Aphasia and hemiparesis which cleared up in three days.
4	60	Diabetes mellitus internal carotid aneurysm	Carotid	Hemiparesis lasting thirty minutes.
5	54	Subarachnoid hemorrhage	Carotid	Seizures — Aphasia and hemiplegia lasting 10 minutes.
6	58	Arterial hypertension Cerebral arteriosclerosis	Carotid	Transitory hypertension.
7	60	Carotid sinus sensitivity Arterial Hypertension	Carotid	Syncope after injection and hemiparesis which lasted 3 days.
8	46	Convulsive disorder	Carotid	Seizures followed by hemiplegia which recovered completely after 30 minutes.
9	38	Hypertensive cardiovascular disease	Carotid	Transient episode of confusion.
10	47	Metastatic brain tumor	Carotid	Patient became less responsive and comatose and expired the following day. Metastasis and marked brain edema at the autopsy.
11	42	Subdural hematoma	Carotid	Transient dysarthria.
12	56	Internal carotid thrombosis	Carotid	Increased hemiparesis.
13	65	Subarachnoid hemorrhage Diabetes mellitus Arterial hypertension	Carotid	Previous right carotid arteriogram with no untoward effects. Following injection patient became semicomatose and developed right hemiplegia, returning to the prearteriogram status in 3 weeks.
14	51	Anterior cerebral aneurysm	Carotid	Transitory hypertension.
15	56	Metastatic brain tumor	Carotid	Hypotension and transient hemiplegia.
16	62	Metastatic brain tumor	Carotid	Transitory hypertension.
17	63	Diabetes mellitus Cerebrovascular insufficiency	Carotid	Transitory state of drowsiness and dysphasia.
18	63	Metastatic brain tumor	Carotid	Focal motor seizures.
19	58	Internal carotid thrombosis	Carotid	Temporary dysarthria and expressive aphasia.
20	43	Anterior cerebral aneurysm	Carotid	After the second injection the patient became unresponsive, had divergent strabismus and bilateral Babinski sign, recovering completely in approximately one hour.
21	54	Internal carotid aneurysm	Carotid	Hemiplegia which cleared up in two days.
22	56	Arterial hypertension Cerebrovascular insufficiency	Vertebral carotid	24 hours after arteriography patient became less responsive and expired two days after. Autopsy showed occlusion of the internal carotid and cerebellar hemorrhage.
23	60	Cerebral arteriosclerosis Diabetes mellitus	Carotid	Patient became comatose and hemiplegic following the third injection. Expired nine days after. No autopsy.
24	46	Brain tumor—Glioma	Carotid	Transitory hypotension.
25	60	Diabetes mellitus Cerebral arteriosclerosis	Carotid	Patient became confused, dysarthric and hemiplegic, downhill course expiring eight days after. No autopsy.
26	58	Cerebrovascular insufficiency	Subclavian	Pneumothorax

in 1,822 injections of 50 percent Hypaque in 540 patients. It is interesting to observe that eight out of the twenty-six patients in whom complications occurred were harboring brain tumors and six of these were metastatic. The hypertensive, atherosclerotic, diabetic patient likewise seems to be a poor risk for angiography. These figures were accumulated from a series of 708 arteriograms on 540 patients between July 1956 and July 1959. 144 of these patients were suspected of having atherosclerotic vascular disease on the basis of clinical observation. In this group, only 80 showed positive angiographic evidence of this condition, the remaining being either negative or revealing other conditions. Of the 80 patients whose angiograms were positive, 26 had occlusion of one or both internal carotid arteries, and 14 had segmental partial occlusions. the remaining 40 positive showed either diffuse disease or occlusion of intracranial vessels. This corresponds closely with a series of 174 patients recently reported by Murphy and Miller[19] in which 43 showed either partial or complete occlusion.

While many cases of vascular insufficiency have been improved symptomatically by long term anticoagulant therapy, it seems more reasonable to attempt restoration of the circulation in those cases where angiographic studies show this to be feasible. The following two cases illustrate different problems where surgical treatment has seemed justified from the results obtained.

CASE SUMMARY

CASE 1-826291

49 year old white man admitted to Henry Ford Hospital April 7, 1956, with a four year history of failing vision in the left eye and progressive mental deterioration. In the year prior to his admission he had repeated episodes of confusion, in which he lost contact with his surroundings for ten to fifteen minutes. One week prior to his admission he had a sudden onset of temporary aphasia and confusion.

General physical examination was essentially normal. Chest clear. Heart sounds regular; no murmurs. Blood pressure 150/90. On neurological examination the patient, who was left-handed was oriented but somewhat obtunded. He had moderate expressive aphasia and right facial weakness. Systolic bruits were heard over both carotid arteries. The balance of the neurological examination was essentially normal. Laboratory tests showed blood count, urinalysis, fasting blood sugar, and NPN, within normal limits. Lumbar puncture showed normal pressure and clear, colorless spinal fluid, containing 86 mgms.% of total protein. The electroencephalogram was essentially normal. Chest and skull films were negative.

Bilateral carotid arteriograms performed three days after admission revealed thrombosis of both internal carotid arteries. On the left side there was no definite collateral circulation to the brain via the ophthalmic artery. The right side showed marked narrowing of the proximal portion of the external carotid artery, although the internal cerebral circulation filled via the ophthalmic artery on this side and the right vertebral artery.

On April 23, 1956 the right carotid artery was explored and a by-pass homograft was placed from the common carotid artery to the external carotid, by-passing the marked narrowing of the proximal portion of the external carotid artery. The patient

had a satisfactory postoperative course and was discharged on April 28, 1956.

He was admitted to the hospital one year later for progress carotid arteriograms which showed patency of the by-pass homograft and good intracranial filling through the ophthalmic artery. At that time his condition had improved definitely. He had only occasional episodes of loss of memory, lasting a few minutes, no visual difficulties, and his neurological examination was essentially negative except for the right facial weakness noted initially.

He was started on anticoagulants in September 1957 in spite of the fact that he was asymptomatic. He was last seen in June 1959 at which time his examination was essentially normal and he stated that he had been working a 12-hour day shift as a bulldozer operator. His memory was good and he had no significant symptoms. (FIGS. 2, 3, 4).

Figure 2

Case I — Right carotid arteriogram showing occlusion of the internal carotid artery above the bifurcation in the neck and narrowing of the proximal portion of the external carotid.

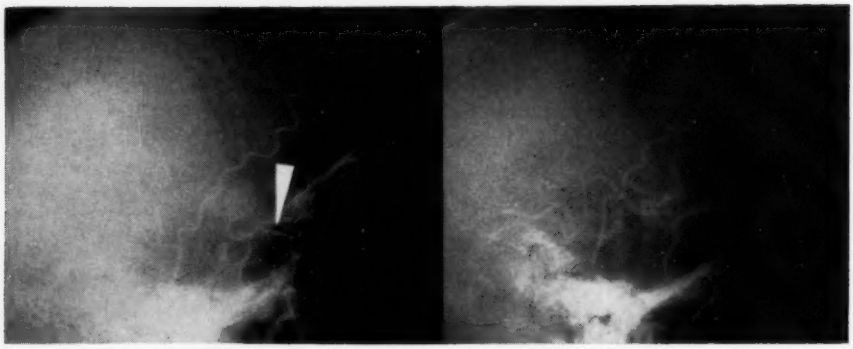


Figure 3

Same case showing filling of the intracranial circulation through the right ophthalmic artery (arrow).

COMMENT:

In this case with bilateral internal carotid occlusion, the intracranial circulation was maintained by the collateral circulation of the right external carotid into the ophthalmic artery as shown in Fig. 3. The proximal portion of the right external carotid showed marked narrowing. It was considered that in order to maintain adequate flow through the collateral system, by-pass of the stenosed area by means of a graft was indicated. The result obtained with this procedure has been satisfactory as evidenced by the patient's clinical course.

CASE SUMMARY

CASE 2-475548

58 year old white man admitted to Henry Ford Hospital on May 6, 1959. Two years before he had a "stroke" with paralysis involving the right side of the body, more so in the face and arm. The paralysis gradually cleared up entirely. Since then he has had recurrent episodes of "a curtain" dropping in front of his eyes, either one, or occasionally both at the same time. Two months prior to his admission he had an episode of complete blindness in the left eye for approximately 20 minutes and his vision gradually returned from the upper field down in 2 or 3 minutes. Since this latter episode he has had repeated transient episodes of blindness in the left eye.

General physical examination revealed a malnourished, chronically ill appearing man. Grade II arteriosclerotic changes were noted in the eye grounds. Lung and heart examination were normal. Blood pressure was 140/80. On neurological examination there was minimal central facial weakness on the right side, and slight, mild residual weakness in the right arm. A harsh bruit was present over the left carotid artery in the upper part of the neck with a softer bruit at the base of it and the pulse in the left carotid artery seemed to be diminished as compared with the right. Visual field examination was normal. Ophthalmodynometer measurements revealed a systolic pressure in the right eye of 90 and a diastolic pressure in the right eye of 45. In the left eye the systolic pressure was 60 and the diastolic 25.

Blood count, urinalysis, fasting blood sugar, urea nitrogen and total cholesterol within normal limits. STS non-reactive. Chest and skull films were negative.

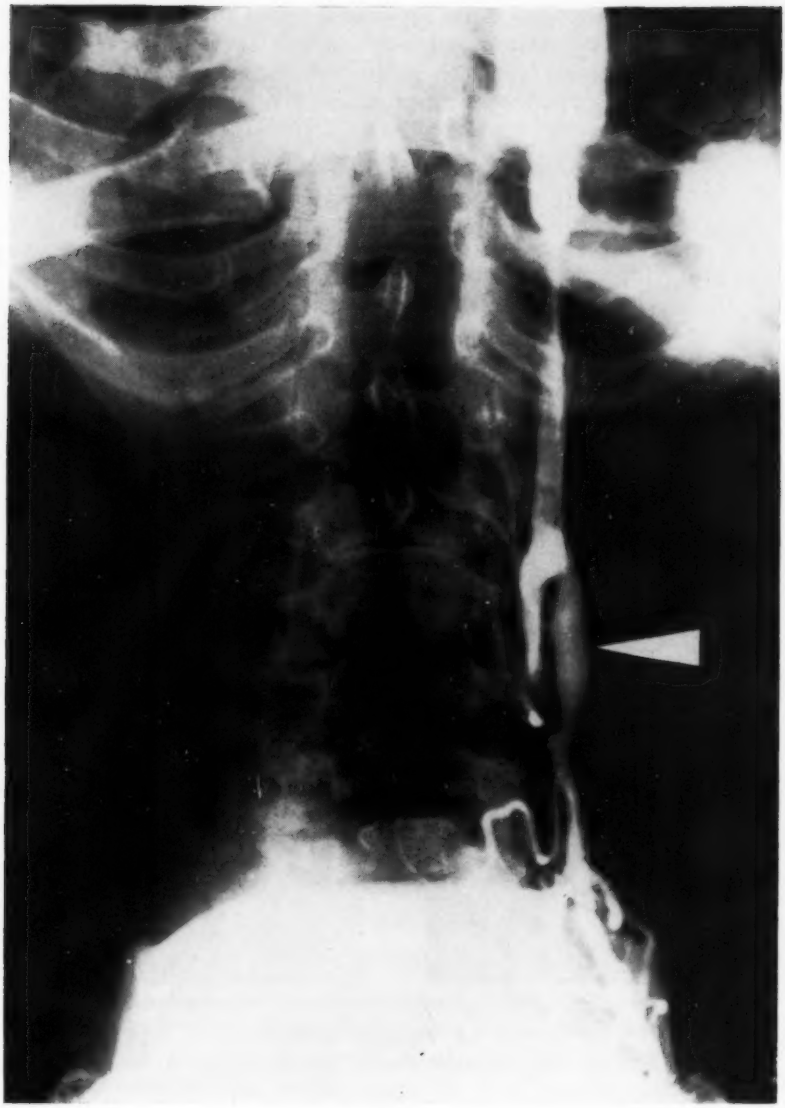


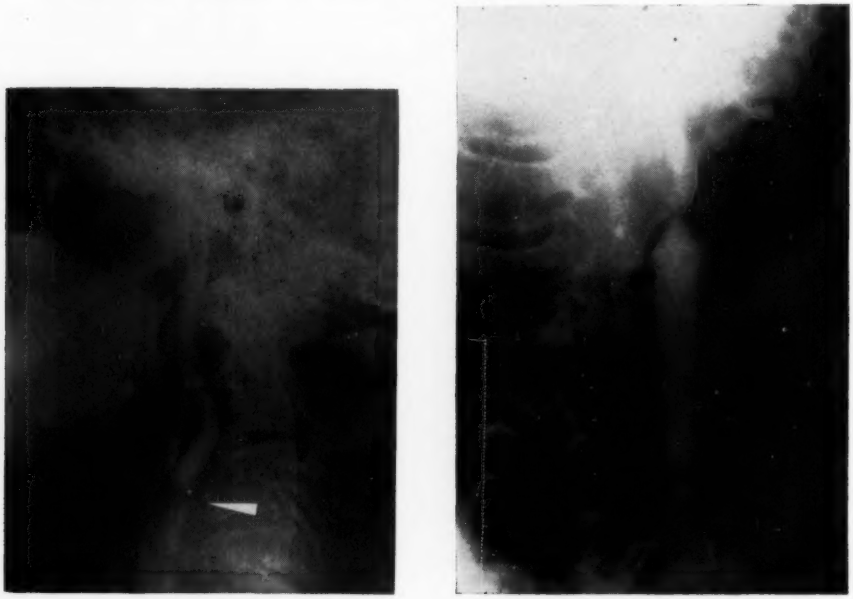
Figure 4

Carotid arteriogram showing patency of by-pass homograft one year postoperative.

Patient was seen by the Neurosurgical Service on May 12, 1959 and the following day a left carotid arteriogram and right subclavian arteriogram were performed which revealed a segmental partial occlusion of the left internal carotid artery. This lesion was considered for surgical removal and on May 15, 1959, under

local anesthesia, endarterectomy of the left internal carotid artery and carotid bifurcation was performed. Following surgery a left carotid arteriogram showed complete filling of the internal carotid artery. The patient had a satisfactory postoperative course and four days later, on dynamometry, the right eye showed a systolic pressure of 120 and diastolic of 50, and the left eye a systolci pressure of 110 and diastolic of 60. He was discharged on May 20, 1959.

He was readmitted to the hospital on June 26, 1959, at which time he stated that his condition had been satisfactory and he was having no further visual difficulties. On examination, no bruits were audible in the neck and the previously noted right facial weakness and mild paresis of the right upper extremity was still present. On June 27, 1959 a left carotid arteriogram was performed which revealed good filling of the internal carotid artery with no evidence of the previous stenosis, which had been corrected by endarterectomy. (FIGS. 5, 6).



Lateral view

Antero-posterior view

Figure 5

Case II — Marked stenosis of the left internal carotid artery above the bifurcation.

COMMENT

The symptomatology in this patient was due to an obvious segmental occlusion with resulting ischemia. Simple removal of the obstruction relived the symptoms.

CONCLUSION

In order to make a definite diagnosis in patients with symptoms suggestive of cerebrovascular insufficiency, it is necessary to study both carotid and vertebro-basilar circulation by means of angiography. With this information at hand it is possible to

Figure 6

Left carotid arteriogram six week after endarterectomy.

be more objective about the future management of the patient. At the present time our studies indicate that stenosing lesions of the carotid artery may best be treated surgically, while insufficiency syndromes related to vertebro-basilar circulation are less likely to fall within this group.

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THE FAMILIAL OCCURRENCE OF HYPERPARATHYROIDISM

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In recent years, the medical literature concerning primary hyperparathyroidism has consisted mostly of an evaluation of new diagnostic procedures and a description of clinical states such as peptic ulcer and acute pancreatitis which may be associated with parathyroid tumor. Less attention has been given to the natural history and pathogenesis of the disease. Several authors, however, have reported a familial occurrence of hyperparathyroidism. In preparing our own recent report of such a case, we came to believe that a compilation of all such instances would prove to be both timely and useful.

Of particular interest to us was a note in Mandl's original case report[1] that a sister of his patient suffered from localized osteitis fibrosa. Although this, of course, does not justify a diagnosis of familial hyperparathyroidism, it raises the possibility that the first diagnosed case was such an example. The first proved case of familial hyperparathyroidism was described by Goldman in 1936.[2] He reported the occurrence of giant cell tumors and parathyroid adenomata in a brother and sister. It is of further interest that the male patient relapsed 10 years after his original surgery[3] again developing a giant cell tumor. Re-operation demonstrated an adenoma in a parathyroid gland previously described as normal.

In 1947, Schneider et al[4] described the cases of two cousins with osteitis fibrosa both of whom were found to have oxyphil adenomata. The next year, Shallow[5] described hyperparathyroidism occurring in a father and daughter with the clinical manifestations mainly in the skeletal system. The symptoms recurred in the father 15 years after the original surgery and another adenoma was removed.

Hyperparathyroidism occurring in 5 siblings of a large family was reported by Frohner in 1954.[6] The father of these subjects had died of a disease manifest by renal failure, polyuria, nocturia, kyphosis and weakness. The mother, two additional siblings and 7 children of the affected members were free of disease. Multiple adenomata were present in 4 of these 5 cases.

The combination of hyperinsulinism and hyperparathyroidism was reported by Moldawer et al,[7] in 1954. The patient was a girl whose father had hyperparathyroidism and peptic ulcer. In both subjects, multiple parathyroid adenomata were removed, although the father's disease was not cured by the operation. Nielsen[8] in 1955, described the cases of two sisters with hyperparathyroidism, the older of whom had mental changes in addition to renal and bone involvement. The psychic disorder was relieved by parathroid surgery. In the younger sister, however, no adenoma could be found at operation.

Careful evaluation of an entire family was reported by Jackson in 1959.[9] The initial diagnosis in this family was made in the course of an acute episode of recurrent pancreatitis. A diagnosis of hyperparathyroidism was subsequently established in 5 siblings and in the two sons of one of these subjects. Two additional sisters and 6 other children of proven cases were found to be free of the disease.

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In view of the foregoing reports, it was no real surprise that Snapper et al,[10] were able to find primary hyperparathyroidism occurring in identical twins. Although the adenomata of both twins were of the same histologic type, the clinical manifestations of the disease were somewhat different. In addition, one twin suffered from sarcoidosis, complicating the problem of differential diagnosis.

Caylor[11] reported hyperparathyroidism occurring in a father and son in 1958, and in 1959, we described hyperparathyroidism in a mother and daughter.[12] The latter relationship had not previously been reported. The mother was known to the medical literature having been described by Hanes[13] as one of the first fatal cases of parathyrotoxicosis. The daughter was admitted to our hospital many years later for the treatment of recurrent pyelonephritis and nephrocalcinosis. Her parathyroid tumor was successfully removed.

DISCUSSION

We have found in the literature 10 instances of familial hyperparathyroidism representing a total of 28 cases. The pertinent available data of these cases have been tabulated in Table 1. The following conclusions seem justified:

Age: The statment by Snapper that familial hyperparathyroidism seems to manifest itself at an earlier age than does nonfamilial disease is supported by this review of the literature. It is likely, however, that a search for the disorder has been made in many of these cases at an earlier age than in patients without such a family relationship. Presumably hyperparathyroidism is often a chronic disease of very long standing and the presence of a known case in the family may provide the clue leading to early diagnosis. On the other hand, the phenomenon of anticipation is well known in other familial disorders and may prove to be a feature of hyperparathyroidism.

Sex: There is no predominance in either sex, the ratio of female to male being 15 to 13.

Heredity: The disease has occurred in either the father or the mother of children of either sex. On the basis of his study, Jackson concluded that inheritance was due to an autosomal dominant gene. However, there are few studies to demonstrate the striking heredity features reported by Jackson. In other familial occurrences, it appears either that penetrance is incomplete or that multiple factors are involved.

Location and numbers of adenomata: As Snapper observed previously, familial parathyroid adenomata often involve glands at the same location. This was true in 5 of the 7 instances which could be analyzed. A striking feature is the frequency of multiple adenomata usually occurring in 6 to 10% of hyperparathyroidism, but reported in 9 of 22 cases analyzed or 41% of this total series.

Recurrence: As reported recently by one of us (G.L.)[14] recurrence of hyperparathyroidism is a very rare phenomenon. However, there are two recurrences in this group of cases, occurring 10 and 15 years after the initial operation. These noteworthy observations of multiple adenomata and relatively frequent recurrences strongly support the concept of an inherited tendency in adenoma formation in this group of patients.

Histology: The available data suggests that the cell type of the adenomata in related cases tends to be the same. Information is incomplete, however, and does not justify a final conclusion.

Calcium level: Again these data confirmed the statement by Snapper that the calcium levels of patients with familial hyperparathyroidism tend to be higher than those of isolated cases. Eleven of 26 cases analyzed were found to have serum calcium exceeding 15 mg. per cent. This marked elevation of the serum calcium level may also help explain the apparent earlier occurrence of the disease, for the disease may be more severe than in the average isolated case.

Clinical manifestations: We have been unable to confirm the concept that osteitis fibrosa is the most likely clinical manifestation of familial hyperparathyroidism. Renal involvement was equally common in this group of cases. Furthermore, as the concept that recurrent peptic ulcer or pancreatitis may be manifestations of hyperparathyroidism becomes more widely appreciated, additional cases of the familial disorder associated with these digestive abnormalities may be discovered.

TABLE 1. FAMILIAL INSTANCES OF HYPERPARATHYROIDISM.

Author	Age*	Sex	Relation	Location of Adenoma	No.	Histology	Ca. level	Manifestation**
Goldman	23	M	brother	LLP, RLP	2	chief cell	16.1-18.6	B, R
	17	F	sister	LLP	1	wasserhelle	19.2	B, R
Schneider	20	F	cousin	L lobe	1	oxyphil	18.3	B
	—	F	cousin	—	—	oxyphil	—	B
Shallow	35	M	father	LLP, subst.	2	oxy. chief	13.0-15.8	B, R
	14	F	daughter	LLP	1	chief cell	15.4	B
Frohner	25	F	sister	RLP	1		15.7	B, R
	25	F	sister	RLP, LUP	2		14.4-19.5	B, R
	29	M	brother	LLP, RLP	2		13.3-13.6	R
	30	F	sister	LUP, RUP	2		16.8-18.1	R, B
	26	F	sister	LUP, RUP	2		15.8	R
Moldawer	22	F	daughter	RUP,LLP,LUP	3		11.6-12.8	R
	36	M	father	LUP, LLP	2		12.1-13.7	U, B
Nielsen	47	F	sister	LLP	1		14	R, B
	33	F	sister		—		14	R, B
Jackson	53	F	mother	RLP	—	chief. oxy.	12.2	P?
	29	M	son	RLP	1	chief. oxy.	13 - 14	P
	27	M	son	RLP	1	chief cell	13	P, B
	47	M	brother	RUP	1		11.8-12.4	B
	40	M	brother	—	—		—	?
	34	M	brother	—	—		12.5	R.B.
	29	F	sister	RLP, L?	2		12.7	B, R
Snapper	33	M	twin	LUP	1	wasserhelle	13.4-15	R
	35	M	twin	LLP	1	wasserhelle	15.5	B
Caylor	31	M	son	LLP			12.2	R
	55	M	father		1	chief cell	12.0	U
Laubinger	49	F	mother	LLP	1	cystic	22	R, B
	42	F	daughter	RLP	1	oxyphil	13.9	R

*Age at time of diagnosis.
**Manifestation: R= renal; B= bony; U= ulcer; P= pancreatitis.

SUMMARY

Although the cause of primary hyperparathyroidism is unknown, heredity seems to be a factor of some importance. Ten instances of familial disease involving a

total of 28 cases have been described in the literature. In these cases, multiple adenomata and true recurrence of the disease have been unusually frequent. The location and histology of the adenomata of related patients is often similar. The serum calcium level tends to be elevated to a more severe degree than occurs in nonfamilial cases, but no particular clinical picture characterizes the related cases. Evaluation of family members of other patients with proved hyperparathyroidism would prove of value to extend and verify these observations.

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RECENT CONCEPTS ON SKELETAL MUSCLE STRUCTURE AND CONTRACTION

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Active investigation in the past decade has clarified many aspects of muscle physiology — The kymograph and light microscope have yielded to more sensitive measurement by x-ray diffraction and the electron microscope. With rapid advances in physics, mathematics and thermodynamics, a greater understanding of the structure and function of skeletal muscle has resulted.

This paper will review some of the recent work describing the ultrastructure of the muscle fiber, its physical changes during contraction and the mechanism thereof. Few of the current theories are entirely undisputed, but in general, the most widely accepted ideas are presented.

STRUCTURE OF SKELETAL MUSCLE

In traditional histology nothing is said about tissue structure beyond what can be observed with the light microscope. Skeletal muscle fibers are described as cross-striated by dark *A (anisotropic) bands*, alternating with light *I (isotropic) bands*.

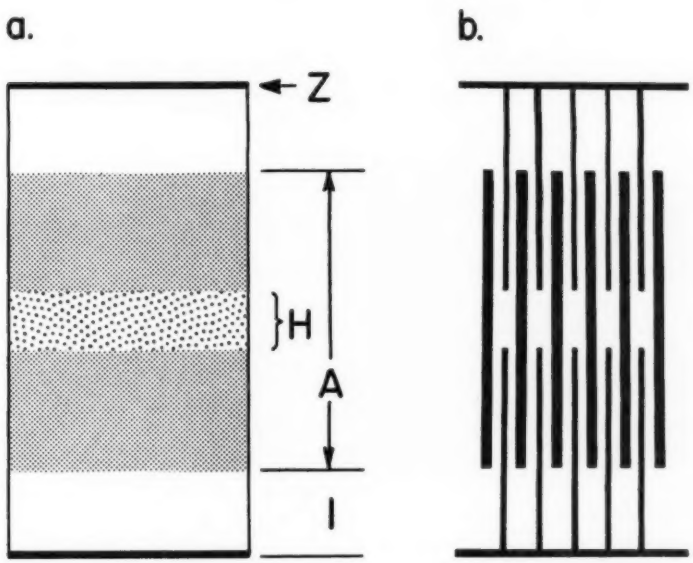

Figure 1

a. Diagram of a sarcomere of a myofibril. The darker A Band is transected by the lighter H zone and the I Band by the Z line.

b. The filaments of a myofibril, as prepared by Huxley, are related to the bands in diagram a. The thick myosin fibrils occupy the A band and the thinner actin fibrils extend from the Z line to end at the H zone.

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Each of these is bisected by a contrasting stripe: the A bands by the light *H zones,* and the I bands by the dark *Z lines.* (Figure 1 a) A good histologist can also distinguish the finer *myofibrils,* running the length of the fiber.

The light microscope, however, has long been perfected to its theoretical limit. It is impossible to build one that will have more resolving power than the best instruments of today. If one is to see more, he must turn to electromagnetic energy of a shorter wave length than that of visible light. The electron microscope is one such refinement. Under it, the striations were seen to be a property of the myofibrils themselves. These delicate threads are aligned with such precision that the stripes appear to be continuous across the width of the whole muscle fiber.

Nevertheless, this is gross anatomy compared to the later developments. Newer microtechniques have permitted scientists to make sections of even the myofibrils. This has revealed that the myofibril itself is a bundle of still finer filaments. Huxley used a special method of embedding and cut the tissue with a glass knife. In this way he has produced slices of muscle only 100 A° thick. This is of the order of magnitude of a single protein molecule. His work has shown that there are not one but *two* kinds of filaments in the myofibril: thick ones and thin ones, both lying parallel to the axis of the muscle. Thick filaments occur only within the confines of the A band. Thin ones occupy the I band and partly intrude into the A band, but halt before the latter's central portion, leaving the lighter "H zone" between their ends. (Figures 1 b and 2). Phase contrast microscopy and x-ray diffraction studies have provided further evidence for this concept.

BUILDING MATERIALS OF MUSCLE

Biologists have known for some time that the chief proteins in muscle are actin and myosin. This information has gained new significance since Huxley's discovery, for the two proteins can now be localized within the cell. If one extracts the myosin from a muscle, the A bands disappear, and with them the thick filaments. This and other evidence strongly implies that the thick filaments are myosin. The A bands owe their anisotropy to their content of myosin, which has greater ability to polarize light than actin. The remaining thin filaments are presumed to be actin, as this is the other major protein.

Actin and myosin are rather remarkable substances. If they are mixed together in solution, there is a sudden rise in viscosity, indicating the formation of the complex, *actomyosin.** Then, by manipulating the ion content of the solution, this complex can be made to settle out as a fluffy cloud. However, if ATP is added, a dense pellet forms instead, suggesting that a rudimentary contractile phenomenon has occurred.

Threads of actomyosin can be prepared. These might be thought of as "artificial myofibrils"; for, in the presence of ATP, they contract much like a living muscle. The molecules of the thread are only crudely oriented by the process of preparation, however, so it is much less efficient than a muscle or even a natural myofibril.

*Probably identical with the "myosin B" of older literature.

Another challenging fact is that actomyosin and myosin have the ability to catalyze the splitting of ATP, liberating its high energy phosphate bonds. Interestingly, ATP in muscle appears to be part of the actin molecule.

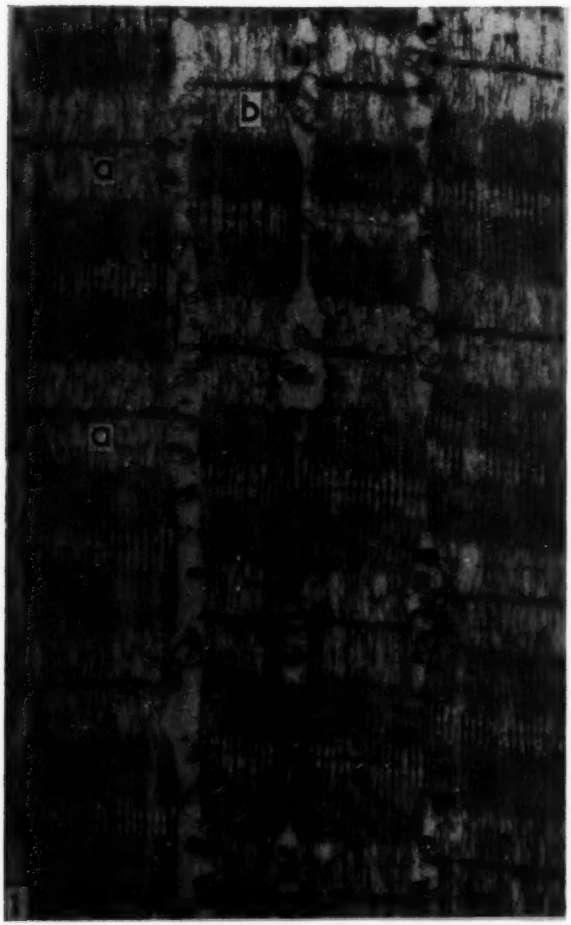

Figure 2

Myofibrils cut in very thin sections and demonstrated by the electron microscope (glycerated rabbit psoas). Their alignment has been slightly disrupted by sectioning, but the cross striations are clearly shown, as are the Z lines and the thick and thin filaments. (From H. E. Huxley, 1957, reproduced with permission from the Journal of Biophysical and Biochemical Cytology x60,000).

MECHANISM OF CONTRACTION

In proposing any theory, it is often wrong to apply the concepts of one order of magnitude to another. For instance, the galaxies are not significantly affected by the viscosity of outer space, while terrestial physics seldom need concern itself

with Newtonian attraction between earthbound objects. Likewise, submicroscopic bodies belong to still another realm. For molecules, "tensile strength" and "elasticity" probably have an entirely different meaning than they do for macroscopic objects. Another pitfall is the tendency to explain a natural phenomenon by some currently popular mechanism.

One of the early theories was that of Weber in 1846. He postulated that a muscle is an elastic body that can change its modulus of elasticity when stimulated. A physicochemical change was thought to occur which caused an increase in elastic tension, with resulting contraction. This was refuted thirty years ago, when it was finally possible to apply the techniques of thermodynamics. A muscle allowed to shorten and do work produces more heat than one contracting isometrically. According to Weber's hypothesis, an isometric contraction should have transformed more of the potential energy into heat, whereas it obviously did not.

In the last several decades, investigators have given more attention to the submicroscopic contractile units within the myofibril. So minute are they that it becomes meaningless to classify their behavior as chemical or physical, for it is both. The only point in common among the many theories advanced is that intermolecular reactions must somehow be oriented so as to cause a unidirectional pull rather than an overall shrinkage.

The Contribution of Thermodynamics: This line of investigation has proven very fruitful in the study of muscle. To begin with, it easily solved the old riddle of whether contraction or relaxation is the active phase of the cycle. Some had felt that energy was required to stretch the muscle as it lengthened, and that on stimulation it merely snapped back to a contracted resting state. It is now known that a contracting muscle produces more heat than one which is relaxing. Furthermore, if a muscle to which no load is attached is stimulated, it contracts and remains short. The small effort needed to pull it back to its resting length bears no relationship to previous or subsequent contracting force. Thus relaxation is an entirely pasive process.

It is now possible to measure temperature changes of a few millionths of a degree occurring in several milliseconds. This has enabled such men as A. V. Hill to define clearly much of the thermodynamic behavior of muscle. Hill has shown that a muscle increases or decreases its total energy expenditure according to the work required of it. In lifting a small load, then, the unused potential energy is not wasted as heat. Surprisingly, the amount of heat liberated depends only on the distance shortened, regardless of the load. The tension developed is also a function of the speed of shortening; for the more slowly a muscle contracts, the harder it can pull.

The Contribution of Optics: What happens to the striations during contraction? This simple question was a highly controversial issue for a long time. To provide an answer, it was not enough merely to eliminate artifacts in the preparation of the tissue. It was also necessary to avoid stimulating the muscle in the process. The interference microscope greatly simplified all this. As a result, it is now generally accepted that the width of the A band does not change during contraction or

relaxation, at least over the physiologic range. The shortening of a muscle fiber is due to narrowing of the I bands. Concurrently, the H zone dwindles and disappears. Somehow the contents of the I band are "absorbed" into the A band. This important discovery suggested to Huxley that contraction is due to progressive overlapping of the interdigitating thick and thin filaments. The actin filaments slide deeper into the A band, between the myosin filaments, until the H zone is obliterated. (Figure 3).

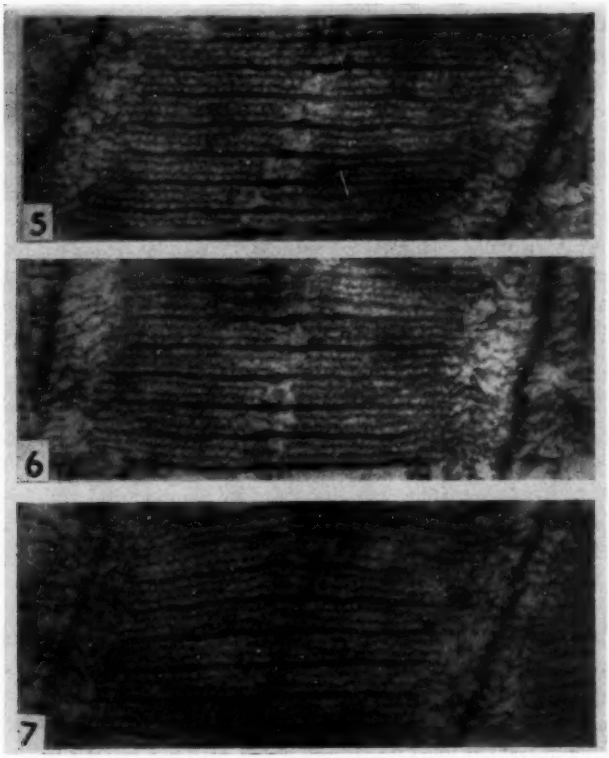

Figure 3

Sections through myofibrils in various stages of contraction. The resting myofibril[5], an intermediate stage[6], and the contracted myofibril[7] (Glycerated rabbit psoas). (From H. E. Huxley, 1957, reproduced with permission from the Journal of Biophysical and Biochemical Cytology x100,000).

The physicist speaks of *form birefringence* and *intrinsic birefringence*. The first is the ability of a particle to polarize light by virtue of its overall configuration: that is, whether it is more rod-shaped or more disc-shaped (Spherical ones have no form birefringence). Intrinsic birefringence is that due to its *substructure*. By suspending the particles in fluids of different indices of refraction, the two kinds of birefringence can be measured separately. This of course gives information as to the shape and substructure of the particle as a whole. Applying a similar technique to actomyosin

threads, it was shown that the form birefringence does not change during contraction. This is evidence that the components of the thread, and presumably those of the myofibrils, do not change their axes. Therefore, they do not fold, as Szent-Györgyi had thought, nor do they coil. The findings are more consistent with Huxley's concept, in which the actin and myosin filaments remain parallel at all times. X-ray diffraction studies have also strenghtened this viewpoint.

THE SOURCE OF ENERGY

Most investigators believe that ATP and perhaps creatine phosphate are the immediate sources of energy for contraction. These unstable compounds can quickly donate their energy to the contractile units. They are re-formed by means of slower reactions, possibly even while the muscle is contracting.

There is a second function performed by ATP which does not involve its breakdown. Whole ATP behaves as a lubricant or *plasticizer*. Without plasticity a muscle could neither contract nor relax, any more than if it were frozen. Experimental removal of ATP prevents a contracted muscle from relaxing. The probable cause of rigor mortis is post mortem destruction of the ATP remaining in muscle. The more active a muscle has been just before death, the less ATP and related compounds remain, and the more quickly rigor mortis appears.

UTILIZATION OF ENERGY

How is energy transmitted from ATP to the myofibril? It is probable that ATP is a part of the actin molecule, and the neighboring myosin can catalyze the hydrolysis of ATP. This spatial limitation restricts the chemical reaction to a single axis, giving *direction* to it. Also, the rate of ATP breakdown is a function of the speed of contraction. All of this can be fitted to Huxley's concept of the structure of muscle. If one examines his photographs very closely, it is apparent that the filaments are not simply straight lines. There seem to be small projections along the myosin filaments at regular intervals. They are probably not artifacts, because x-ray diffraction studies demonstrate similarly spaced interruptions in continuity. Huxley interprets these as intermolecular bridges, or appendages, by which the myosin filaments can "paddle" their way along the actin filaments, causing them to overlap more and more so that the myofibril shortens. The myosin bridges are thought to form temporary connections with active sites on the actin, pull the filaments a short distance, and release. This cycle is repeated as long as the muscle is shortening. Expressed less presumptuously, the bridges could be said to vibrate; and, because the pull is unidirectional the probability of interaction with the adjacent thin filament must be greater with a bridge on one side of its equilibrium point than on the other. With each interaction, a phosphate group is split from an ATP molecule, providing the energy. The heavier the load the greater the tension, because more bridges are brought into operation. On the other hand, tension is less at higher speeds of contraction, since the limited time permits fewer bridges to contact the active sites and interact with them. This would account for the findings of Hill; that is, the tension developed is a function of the speed of shortening. When

the muscle relaxes, ATP breakdown stops and the bridges release their hold, provided there is a surplus of unused ATP to act as a plasticizer. In the absence of excess ATP, the myosin bridges seize on the actin, resulting in rigor mortis.

Cogent as it is, one cannot definitely say that Huxley's theory of contraction is the most probable. Some have conceived of a set of contractile elements lying end to end in the myofibril, capable of being reversibly transformed from long to short forms by some chemical reaction. The overall length of the muscle would be governed by the relative rates of the two opposite reactions (Polissar; Varga and Szent-Györgyi). Pryor extended the analogy between muscles and heat engines even to the point of describing a work cycle for muscle. He feels that certain biochemical substances can perform the same function as heat does in an engine, and has demonstrated this experimentally by making tendons contract and relax under the influence of chemicals. Nor has the coiling filament model been discarded. Botts and Morales feel that in resting muscle the filaments are held in extension by electrostatic repulsion between positive ions on adjacent coils. On stimulation negative ATP ions are made available to neutralize the charges, so coiling (and therefore shortening) can proceed. By making other assumptions, they can also reconcile their concept with the thermodynamic observations.

CONTROL OF CONTRACTION

Lastly, let us consider how the motor end plate communicates with the countless infinitesimal working parts under its command. What happens from the moment a muscle is stimulated to the time it contracts? How does it keep from contracting all the time? There are a few partial answers. Other conditions being constant, there is for any muscle a certain concentration of ATP that is optimal for contraction. Deviations on either side of that point reduce the probability of contraction — so much so that a relatively small increase in ATP concentration above the optimal level prevents it entirely. Furthermore, the optimal ATP concentration for a given muscle is not constant but depends on a number of other variables, among which are the concentration of ions such as magnesium.

One can extract from muscle a factor which prevents the "artificial myofibril" from contracting when ATP is added. This *relaxing factor,* or *Marsh-Bendall factor* appears to play a key role in the contraction-relaxation cycle. During rest, it inhibits the breakdown of ATP by actomyosin. Perhaps it does this by binding magnesium, which is necessary for the ATPase function of actomyosin. It is equally possible that it renders the concentration of ATP superoptimal, either by favoring ATP synthesis or by removing available magnesium so that the existing ATP level *becomes* superoptimal. Whatever the mechanism, it seems that magnesium is necessary for both the function of relaxing factor and the ATPase activity of actomyosin. As long as the membrane potential of the muscle fiber is high, the ion remains bound to the Marsh-Bendall factor. When the muscle is stimulated, the resting potential is disturbed and the magnesium is transferred to the actomyosin, enabling it to catalyze ATP hydrolysis, with release of energy. Contraction can then proceed. At the same time, Marsh-Bendall factor combines with calcium, and is inactivated.

SUMMARY

1. Myofibrils consist of thick myosin filaments (A Band) and thinner actin filaments (I Band). Cross bridges are believed to exist between these two protein filaments.

2. During contraction it is likely that the actin filaments slide between the myosin filaments.

3. Actomyosin has both contractile and ATPase functions.

4. ATP serves as a source of energy for contraction and plasticizer during relaxation.

5. In resting muscle, magnesium is joined to the Marsh-Bendall relaxing factor and actomyosin can not function as an ATPase enzyme.

6. On stimulation of the muscle, magnesium is shifted to actomyosin and ATP is hydrolysed with resulting contraction.

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SPASTIC DIPLEGIA OF PREMATURE BIRTH

JOHN A. CHURCHILL, M.D.*

On the basis of differences in neurological findings, patients who have cerebral palsy can be grouped into several forms which are: (1) Athetosis, (2) Hemiplegia, (3) Ataxia, (4) Complex Diplegia, and (5) Simple Spastic Diplegia. The form of cerebral palsy termed "simple spastic diplegia", with which this presentation is particularly concerned, was described and differentiated from Little's disease in a recent publication[1]. Patients who have simple spastic diplegia present the following findings: (1) Spasticity involving both lower extremities equally, the upper extremities being less spastic than the lowers, (2) Impairment of motility, especially of the legs, (3) Delayed onset of walking, (4) Contractures of the heel cords, thigh adductors and hip flexors, (5) Hyperactive deep tendon reflexes, and (6) Positive plantar responses. The findings can be interpreted in terms of bilateral damage to the so-called pyramidal tracts. Extraocular muscle imbalances are commonly found in these cases as in prematurely born infants generally[2]. Patients who have simple spastic diplegia differ from those who have complex diplegia in a much lower incidence and lesser severity of mental subnormality and convulsive seizures. They lack positive tonic neck reflexes, athetoid and ataxic movements, and other manifestations which can only be explained on the basis of extensive cerebral dysfunction.

In our group of 70 patients who have simple spastic diplegia all except 11 were born prematurely. Six of the non-prematurely born individuals were delivered by breech extraction, and probably owe their disability to stretch injury of the spinal cord[3,4].

The distribution of birth weights of the patients with spastic diplegia is shown in figure one. These are compared to the birth weights of a group of patients who have no neurological disease, or have diseases acquired later in childhood; not of early origin. The predominance of cases with spastic diplegia in the lowest birth weight ranges is in sharp contrast to the lack of cases of low birth weight in the group of cases without neurologic diseases of early origin.

The correlation of simple spastic diplegia to low birth weight is even more strikingly demonstrated when the proportions of the cases in different birth weight ranges are corrected for neonatal mortality rates of infants in the different ranges[5] (Figure 2).

The birth weight distribution curves of the other forms of cerebral palsy differ from those of patients with simple spastic diplegia (Figure 3). The birth weight distribution of the cases with complex diplegia reveals a fairly large proportion of the cases with moderately low birth weight, but even so, the curve is clearly distinct from that of simple spastic diplegia.

Groups of patients who have mental subnormality or idiopathic epilepsy differ from the group with simple spastic diplegia in the birth weight distribution curves (Figure 4).

*Division of Neurology and Psychiatry.
Prepared for the Internat. Congress of Pediatrics 1959.

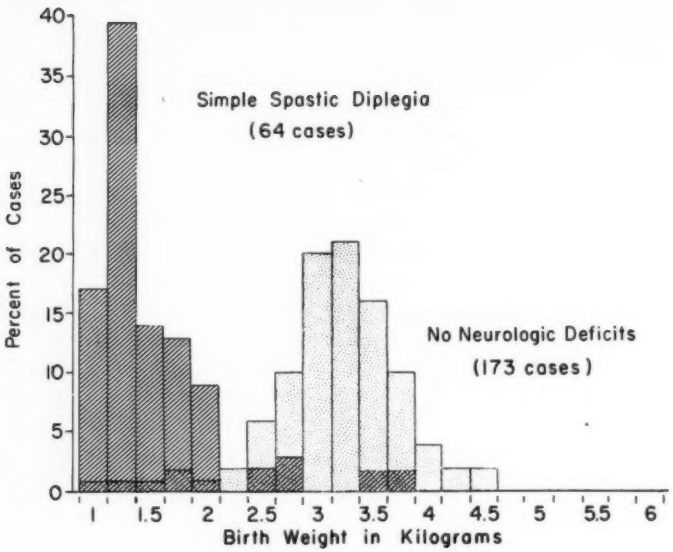

Figure 1

Birth weight and simple spastic diplegia compared to birth weight of normals.

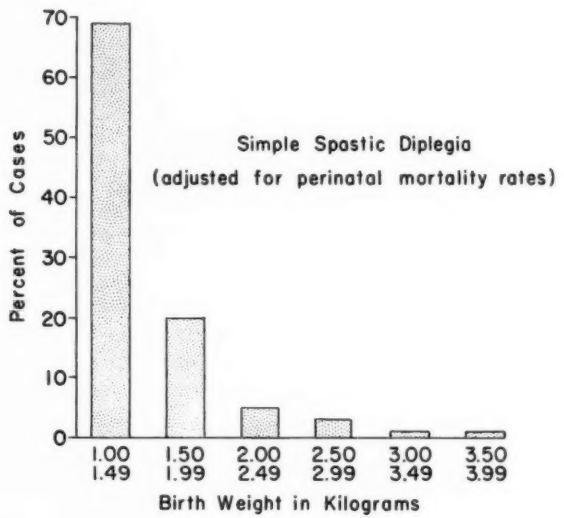

Figure 2

Simple spastic diplegia correlated with birth weight and corrected for neonatal mortality rate.

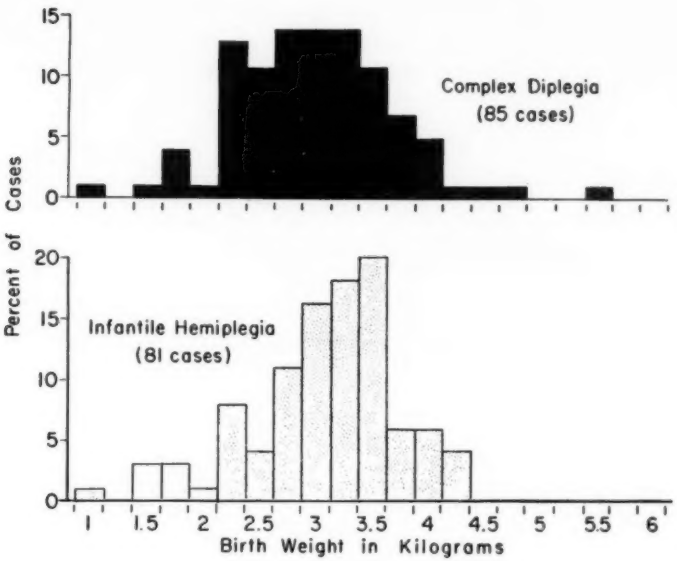

Figure 3
Birth weight by other forms of cerebral palsy.

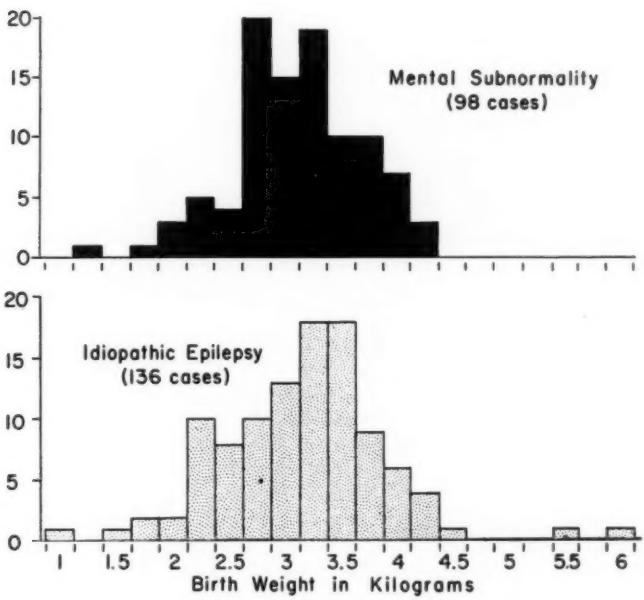

Figure 4
Birth weight by mental subnormality and by idiopathic epilepsy.

Using gestation time as the criterion for prematurity it is again observed that the group of patients with simple spastic diplegia were born prematurely much more frequently than were patients who had no neurological disease of early origin (Fig. 5).

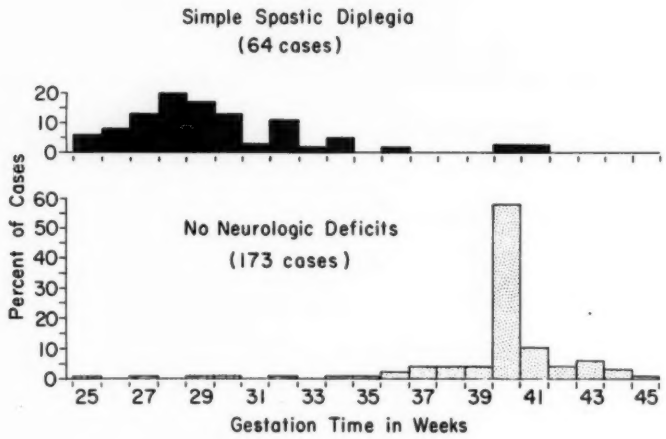

Figure 5
Simple spastic diplegia charted by gestation time.

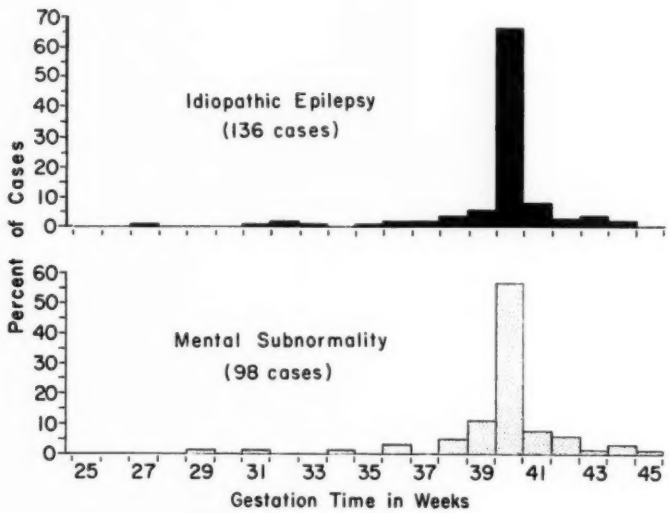

Figure 6
Complex diplegia and infantile hemiplegia charted by gestation time.

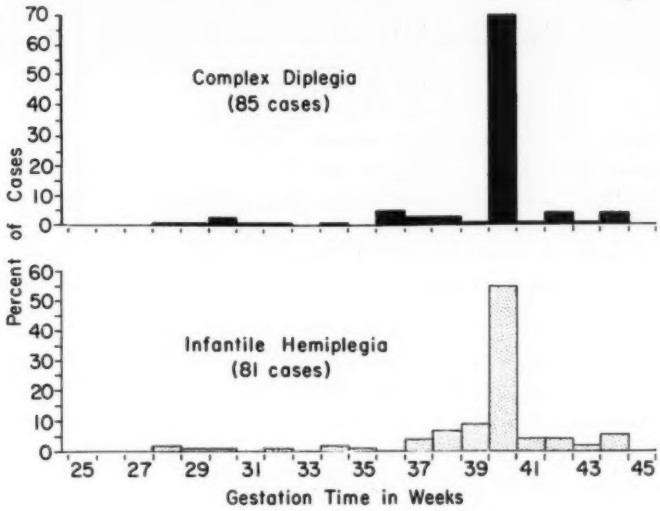

Figure 7

Idiopathic epilepsy and mental subnormality charted by gestation time.

Similarly, gestation times were much shorter in patients with simple spastic diplegia than in those with other forms of cerebral palsy, (Fig. 6) or in cases of mental subnormality or idiopathic epilepsy (Fig. 7).

The correllation of low birth weight, and also short gestation time, to simple spastic diplegia is very strong. No distinct correllation between birth weight or gestation time has been found in the complex diplegic (or quadriplegic), hemiplegic, athetoid, or ataxic forms of cerebral palsy. Neither has a correllation of this magnitude been found between prematurity and mental subnormality or epilepsy.

Spastic diplegia is now clearly established as a disease of the premature infant, and although the pathogenesis of this disease may not be directly derived from prematurity, this form of cerebral palsy can now be defined as spastic diplegia of premature birth.

The possibility that this disease may result from biochemical aberrations in the premature infant is now being investigated.

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A STUDY OF THE REASONS FOR NON-PARTICIPATION IN THE SALK VACCINE PROGRAM

SARA HUGHES, M.S.W.*

The following is a descriptive statistical analysis based on a study of 30 polio patients and their families to determine their reasons for non-participation in the Salk vaccine program. The information was gathered from person-to-person interviews conducted by the interviewer who used a standardized questionnaire. The survey was not designed to probe deeply for underlying factors in motivation, but rather to assess, from the questions asked, the attitudes and opinions of these families toward polio vaccination.

The 1958 Detroit polio epidemic affected most severely the pre-school children under four years and the Negro population as a whole. Also, there were more paralytic cases this year than in any year since the Salk vaccine program started in 1955; in addition, the paralytic status of Negro cases exceeded those of the White group.

In examining the 30 cases studied, the following table shows the age incidence, sex, race, and paralytic status of the polio patient.

Table 5

Age, Sex, Race, and Paralytic Status of 30 Polio Patients

Total	Age Group	Female	Male	Race White	Race Negro	Paralytic	Non-Paralytic
13	0-4	7	6	1	12	12	1
10	5-9	5	5	1	9	5	5
2	10-14	1	1	0	2	2	0
2	15-19	2	0	2	0	1	1
3	20 plus	3	0	0	3	1	2
30		18	12	4	26	21	9

In the age group 0-4, two of the paralytic cases were the bulbar type of polio. The remaining ten in the paralytic group had some type of spinal-paralytic polio.

In the age group 5-9, the paralytic cases were spinal. Two of the children in this group had had two vaccine inoculations but had never been given the third dose.

In the age group 10-14, there was one case of spinal-paralytic polio and one case of bulbar polio. The children in this group were severely disabled, the bulbar case having had to be transferred to the Respirator Unit of University Hospital in Ann Arbor, Michigan. Neither child had had the Salk vaccine.

In the age group 15-18, one was a 17-year-old mother with spinal-paralytic polio and the other was a 19-year-old girl with non-paralytic polio. None had had the polio vaccine.

*Social Service Division.

In the 20 plus age group, all three were mothers, ranging in ages from 30-32. The one paralytic case was spinal in nature. One mother had had two doses of the vaccine, but the other two had never been inoculated.

One of the leading questions in the interviews was: "Did you know of the Salk vaccine program?" Out of the 30 persons interviewed, all but two had known of this program prior to the 1958 epidemic. The sources of information given by the remaining 28 families are listed in the table below:

Table 6

Publicity

Source of Information	Number
Newspapers	17
School	12
Friends	0
Posters and leaflets	0
Radio	3
Television	3
Church	0
Doctor	2
Meetings	0
Other	2

Some informants gave more than one source of information, which accounts for the excess number. The newspaper, given by seventeen, was the most common source. However, the name of the newspaper was not mentioned specifically in any of these cases.

The next common source was the school with twelve. Out of this number, six also listed the newspaper. Those giving the school as the only source were six.

Those mentioning the radio as a source of information also mentioned hearing about the program over their television sets.

As only five families had their own private physician, the doctor did not seem to be a key source of information.

Other sources of information given by two informants were: Health Clinic and a car with loud speakers which combed the neighborhood from time to time.

As many leaflets written about the Salk vaccine had been given by the public schools to children to be passed on to the parents, it was felt that this might have been a source of information, although no person recalled this. The interviewer was of the opinion that in many cases there was such little interest in the program that the informant would not put forth the effort to try to recall various sources of information.

Although the 28 individuals of the 30 families contacted knew of the Salk vaccine, the following table lists the stated reason for non-vaccination.

Table 7

Reasons for Non-Participation in Salk Vaccine Program

	Number
Knew of program	28
Did not know of program	2
No interest in program	0
Fear, uncertainty of vaccine	6
Time and place not clearly understood	3
General opposition to all shots	1
Wrong age group for polio shots	1
Unable to get out (ill or confined by other duties)	9
Cost	10
Vaccine not available	1
Lack of clinics in neighborhood	6

Some of the informants gave several reasons as to why either they or their children were unvaccinated or incompletely vaccinated prior to the 1958 epidemic and subsequent thereto — hence the duplication in numbers.

Other reasons given and comments made concerning the program were:
"I just neglected it — never got around to it."
"My doctor didn't talk much about those shots."
"We didn't know there were free clinics."
"There's too much red tape at clinics."
"I just kept putting it off."

Although no one expressed *No interest in the program,* it seemed a far greater number exhibited this attitude in the interview but gave other reasons instead.

The six persons who mentioned fear and uncertainty of the vaccine further expressed their feelings by stating:
"If you took those shots you were sure to get the polio."
"We knew kids who got real sick after the shots."
"The newspapers even said that people who took the shots died with polio."

The interviewer was of the opinion that there were more than six individuals who feared the vaccine but who were too embarrassed to express their feelings. It was noted that a few informants seemed to be quite defensive in this respect. One adult stated, at the close of the interview, that she might as well confess "she was afraid of that needle."

General opposition to all shots was given by one person who mentioned that her husband and his family were healthy and didn't believe in any vaccinations, and she usually went along with her husband's opinion.

The one adult who thought she was in the wrong age group for polio shots was a 31-year-old mother with spinal paralytic polio, now confined to a wheelchair.

Three mentioned *time and place not clearly understood,* one informant stating that she didn't know the day and time you would be taken at a free clinic.

Unable to get out was expressed by nine persons. Two of the mothers said they were pregnant at the time and did not think of taking the vaccine. Some mentioned being confined at home by illness of their children; others stated that it was difficult to get to clinics or to doctors' offices because of transportation facilities; others mentioned they had no one to watch their children in their absence from the home.

The *Cost* factor was mentioned by ten of the informants, several stating that they thought the doctors charged too much. When questioned as to their knowledge of free health clinics, two or three persons replied that they had never been on charity before and didn't know where to go for free medical services. Several mentioned the unemployment picture in Detroit and how it had affected their economic status.

One person stated that at the time she took her children to the health center, they had run out of vaccine and she had never bothered to check back.

The six who mentioned *lack of clinics in the neighborhood* were not aware that these existed at all.

In general, most of the persons questioned were favorable toward polio vaccination with the exception of the six, who feared the safety and effectiveness of the vaccine, and the one person who was opposed to all shots. However, despite the objections of these persons, all children in the 30 families (exclusive of the polio patient) have now been immunized against polio or are in the process of completing same. In helping to bring this about, much credit can be given to the polio immunization program in the Detroit Public Schools where, since September 1958, the vaccine was given in 243 schools. The majority of these schools are located in the areas covered by this study and the areas most seriously affected by the epidemic.

Table 8 shows the number of persons who had some previous understanding of the nature and prevalence of polio and those who had little or no knowledge about the disease itself.

Table 8

Knowledge about polio	18
Little or no knowledge about polio	12

The majority who knew about polio stated that they had had prior contact with some friend or member of their family who had contracted this disease. One mother mentioned that she had had polio as a child and another mother said that she had come in contact with it while she was employed as a nurses' aide in a hospital.

It was felt that, on the whole, there was little knowledge among the group about the disease entity itself and about any protective measures that might have been suggested in the past. Several persons made the comment: "They didn't know how serious it was." Others referred to the disease as "infantile paralysis," and there might have been a lack of awareness that "polio" and "infantile paralysis" were one and the same disease.

It would appear, also, from responses made to the interviewer, that the lack

of understanding about polio and the value of immunization was not confined to this one disease itself. For example, one or two mothers had confused diptheria or smallpox shots with the polio vaccination, believing that if their child had been vaccinated against one or the other, he or she might be immune to polio.

The interview questionnaire contained several questions concerning the occupation of the wage earner in the family, present and previous economic status of same, and family composition. Table 9 indicates the breakdown of this data.

As indicated in Table 9, eight of the mothers interviewed were separated from their husbands and were receiving either alimony or Aid for Dependent Children, or both. The three unmarried mothers were also on ADC grants, and the fourth was receiving a weekly income from a common-law husband.

Table 9
Family Economy of Study Group

Occupation of Wage Earner	Present Income	Previous Income	No. of Children
Housewife[a]	Receiving alimony and ADC		6
Press operator	$3,400 per annum	Same	5
Crane operator	Unemployed	$150 per week	6
Housewife[a]	Receiving ADC		3
Housewife[a]	Receiving ADC		6
Post office clerk	$3,900 per annum	Same	2
Housewife[b]	Receiving ADC		1
Steel worker	$65 per week	Same	8
Construction work	Unemployed	$100 per week	4
Housewife[b]	Receiving ADC		2
Assembler	$66 per week	$70 per week	6
Sanitation Dept. Laborer	$86.00 per week	Same	4
Mechanic	$60 per week	Same	5
Housewife[b]	Receiving ADC		3
Truck driver	Unemployed	$75 per week	9
Stock clerk	$75 per week	Same	3
Construction work	$90 per week	Same	2
Housewife[b]	$50 per week	Same	3
Car polisher	$86 per week	Same	5
Housewife[a]	Receiving alimony and ADC[c]		5
Mechanic	Unemployed	$80 per week	4
Auto foreman	Employed part time	$6,000 per annum	4
Housewife[a]	Receiving ADC		3
Housewife[a]	Receiving ADC		5
Real Estate	Not furnished		3
Housewife[a]	Receiving alimony		5
Construction work	Unemployed Husband ill	$87 per week	1
Mechanic	Unemployed	$125 per week	1
Mechanic	$3,200 per annum	$5,000 per annum	3
Housewife[a]	Receiving ADC		5

[a]Separated from husband
[b]Unmarried
[c]Aid to Dependent Children Assistance

The wage earners who are presently unemployed are either receiving unemployment compensation or public welfare assistance.

During the interview study, the interviewer rated the quality of the respondent's neighborhood and condition of house. Table 10 identifies the residential status of the 30 families.

Table 10

Type of Neighborhood and Condition of House

	Good	Fair	Poor
Neighborhood	1	15	14
Condition of House	1	12	17

The question dealing with the educational level of the persons interviewed, brought forth no comment nor explanation as to why they had not gone further in school. Table 11 shows grade distribution in the 30 homes.

The interviewer did not find that those persons with more education possessed a better understanding of the nature of polio as a disease and there did not seem to be any correlation between educational status and knowledge about polio.

Table 11

The Educational Level in the 30 Homes

Grade	Number
No training	0
First grade through sixth grade	3
Seventh through ninth grade	11
Completed tenth grade	6
Completed eleventh grade	3
Twelfth grade graduates	6
College graduate	1
	30

Table 12 indicates the number of parents who have had or are now in the process of being vaccinated against polio.

Table 12

Parents Who Have Taken Salk Vaccine

	Both Parents	Neither Parent	Mother Only
Vaccine taken or inoculation in process	5	15	5

Some of the reasons given by mothers for not yet availing themselves of the Salk vaccine were:

Fear about the safety of the vaccine
Too busy with the children
Over-age for polio shots
No time to get the shots
Not sure where the clinics are
Adults are immune to polio

If the fathers were present during the interview, their stated reasons for non-participation in the vaccine program were:

Can't take time out to get vaccinated
Wrong age group or too old
Healthy and have never been ill
Just haven't gotten around to it
Don't know where to go to get vaccinated

Although these parents have had their children vaccinated, some of the factors influencing their decision not to vaccinate themselves were related to procrastination, neglect, apathy, misinformation, or their conception of the safety and effectiveness of the vaccine. Many of them felt that it did not matter whether adults were vaccinated against polio nor were they aware of the severity of polio in their age group.

Table 13 shows the length of time these families have lived in the city of Detroit and their former place of residence. It may be noted in this table that six families had migrated to Detroit from Georgia; three from Mississippi; three from Tennessee; and the other southern regions from which they came were quite evenly dispersed.

Table 13

Geographical Representation of Families

No. of Families	Years Resided in Detroit	Former Residence
13	5-9	3—Georgia
		1—Missouri
		1—New Jersey
		1—Kentucky
		1—Texas
		2—Mississippi
		2—Arkansas
		2—Tennessee
4	10-14	1—West Virginia
		1—Tennessee
		1—Georgia
		1—South Carolina
9	20 plus	

One of the leading questions was: What type of program do you think would be effective towards stimulating others to take the Salk vaccine? Some of the comments made by those favorable toward the vaccine were:

"Give the doctors more vaccine and have them charge less."

"More doctors should give it free of charge or bring the cost down to an amount which people could afford."

"There should be more free clinics."

"More information should be given over the radio and television."

Several mothers stated that there should be more nurses visiting the homes to

talk about polio. One mother referred to a public health nurse as being an instrumental person in getting her and her children to take the vaccine.

Others were of the opinion that nurses should make home calls to give the polio injections.

One father mentioned that after his child had been stricken with polio, he wanted to organize a group in his neighborhood to make calls on others to inform them about the vaccine. He also stated that he had written to the local office of the March of Dimes, offering his services along these lines, but had never heard from them.

Some persons stated that parents should visit hospitals or places where crippled children are so they would realize how serious polio is — that this would really wake them up.

Several referred to meetings as a good place to inform others about the vaccine. They didn't specify what types of meetings should be held, except mentioning the P.T.A. group. Only two mentioned the church as a probable source of information, stating that the local pastor could speak to mothers' groups about the importance of the vaccine.

One mother, who had previously been employed by the Bureau of Social Aid, suggested that the public welfare agencies should stress the vaccination program among the applicants.

One person suggested the vaccine be made compulsory in the State of Michigan.

One mother, who feared the inoculation, said: "If there were some other way besides having to take that needle."

Other comments made were:

"You go along thinking nothing will happen to your family or kids, and when polio strikes, you get shook-up."

"You hear about polio but you don't pay attention until someone in your family has it. This is an eye-opener."

A number of families, although they were favorable toward the vaccine, had no suggestions or ideas, mentioning they needed more time to think about this or they hadn't given it much thought.

It would appear that the majority of persons interviewed seemed to think in terms of personal or "door-to-door" contact as a means of influencing their peer group toward vaccination. Also, the process of informal communication — getting people to talk about the vaccine — seemed to be the method proposed by most of this group which might accelerate the vaccination program.

ALL-INCLUSIVE CARE FOR THE CANCER PATIENT

A STUDY OF SOCIAL FACTORS

BERNICE P. ROWEN, M. S. W.*

Today's cancer patients are presented with some unexpected remissions, thanks to the findings of extensive research in very recent years. Today, patients with advanced cancer are given hope for pain reduction and arrest of the disease to an extent where they enjoy normal activities during much of the time after their condition is diagnosed "advanced".

It is the changed attitude towards the advanced cancer patient that intrigues and stimulates interest in learning why, and how, doctors are being able to project optimism into their attitudes toward the patients who, until so recently, have been classified as "terminally ill".

Is this approach effective? To be effective, what should the doctor know about his patient? How can the gap be bridged between treatment plans, and the "total" patient's tolerance for the treatment, not only physically but emotionally, economically, and realistically? How does this program affect the families of patient?

The sample used for this study was all the expired patients on the Oncology service for the year 1957. Because three of the histories were in use in the x-ray department during the time of compiling this study, they were deleted from analysis.

Since this survey is confined to expired patients on the Oncology service, during the period from January 1, 1957 through December 31, 1957, further reference to "patients" will indicate the patients of this sample. The temporal base will be from the date of entry to Oncology service. These definitions will be observed in order to eliminate repetitious explanations.

Table 1

Total number of expirations on oncology service in 1957

	Total Expirations	%	Records Unavailable	%	Total Sample Used	%
Male	56	36%	2	1%	54	34%
Female	101	64	1	1	100	64
Total	157	100%	3	2%	154	98%

It is interesting to note that there were nearly twice as many women who died as there were men. This does not bear out the figures given on a national basis for the incidence of cancer as distributed between the sexes. Figures from a larger series, show a rate per 100,000 of 250.6 for males, and 273.5 for females. Incidence of cancer is compared more frequently by site rather than by sex, as this is the apparent pathological determinant. Many factors can be related to these skewed figures, the most obvious one being that the sample is not compatible with that of the national incidence.

Table I establishes the group for the study. Since the sex of the patient is not significant to this study, it will not be dealt with. The three medical histories which

*Division of Social Service.

were unavailable were deleted from the sample, leaving 154 cases to be used as a base. This is the use being made of Table 1.

The age of the patient with any chronic illness has more social implications than has sex. The spread of incidence according to age is compatible with that of the national figure.

Table 2

Age of patient when entered oncology service

Patient's Age	No. Pts.	Percent
Under 20 years	7	5%
21 — 40 years	12	8
41 — 60 years	68	44
Over 61 years	67	43
Total	154	100

Though the incidence appears to be related to the age factor, this is not actually the case. Other determinants that are more significant to the incidence of cancer fall within these age categories, such as exposure to environmental conditions. Such factors are, of course, still being studied for their validity. Though we may not know why our patients fell into these age categories, it seems that people over 40 years of age have the highest incidence of advanced cancer.

Socially, this may be interpreted to mean that their chlidren will be either independent, or past the need for close supervision. It may mean that they can expect care at home, since their children will be old enough to help. Those over 60 years of age fall into the national trend of lengevity, having eluded other deadly diseases which science has controlled.

Of all patients in the sample, 87 percent were over 40 years of age. Those between 41 and 60 years, or 44 percent of all patients, were in the period of their lives when their earning power is the greatest; when their family obligations are nearly over; when they are looking ahead to retirement. Economically, this is an important segment, since there should be from five to 25 years of earning power, which chronic illness and probable death will sadly curtail.

Those who were 60 years of age, or 43 percent of the sample, fall into the old age group which is already a large proportion of the country's population, with attending problems. These people, for the most part, are no longer earning, and medical expenses soon deplete their life's savings, unless they have adequate resources.

Table 3

Marital status when patient entered oncology service

Status	No. Pts	Percent
Single	19	12%
Married	114	74
Widowed	11	7
Sep. or div.	10	7
Total	154	100%

The patient's marital status is an important factor socially, economically, and

emotionally. Though the incidence of cancer is not significant as a variable, there would be many other variables which would demand consideration.

Illness in the home carries many connotations, both to the patient, and to the family. The meaning of the illness will vary according to the ages of the individuals involved. Because the professional staff is aware of the dynamics of family life, it is important for those attending the patient to know about each patient's role within his own family.

The significance of the patient's marital status rests in how his status affects his ability to meet the contingencies of illness. Those patients whose primary family group can absorb the realities of illness would be expected to be in the 74 percent which comprises the married persons. Emotional concomitants could skew the figures either way.

Such social information is important to the professional team in order to plan his course of treatment. By knowing how the patient sees his role in his family constellation, one can deduce how he sees his illness, and what his motivation would be for helping in his recovery.

Table 4

Age bracket of patient's children on entry to oncology service

Age of childrne	No. Pts.	Percent
No children	42	27%
Preschool children	7	5
Grade school	20	13
High school or college	6	4
Independent	74	48
No record	5	3
Total	154	100%

Histories were not complete as to full information. The age of patient's children was often omitted. Instead of giving the age of their children, some parents would generalize by saying, "adult", or "grown" or "independent". When the children were small, their ages were usually noted. This tabulation appears to have the categories of *High school and college* and *Independent* skewed, though not significantly for interpretations needed for this survey. By combining the categories of *Preschool children* and *Grade school children,* there is a total of 27 patients, or 18 percent, whose children were under high school age.

The social aspects of the children's ages would be affected by the degree of dependence or independence that they had in relation to the ill parent. If the children are independent, knowledge of this by the professional team would indicate how much family care can be expected for the patient. Professional responsibility would terminate, in these instances, with the death of the parent.

Dependent children pose a different problem for the consideration of the team. Planning for the patient's care also involves planning for the care of the children. The responsibility of the medical social worker extends beyond the life of the patient if the patient's death involves placement of the children, or complicated family situations.

Emotional factors can be expected to run high in the relationships between patients and children. This area is one of which the social worker must be aware.

Table 5

Survival time of patient after entering oncology service

Length of time	No. Pts.	Percentage
Under 30 days	42	27%
31 — 90 days	49	32
91 — 120 days	11	7
121 days — 6 months	17	11
7 months — 1 year	19	12
Over 1 year	13	9
Left service	3	2
Total	154	100%

Patients are not referred to Oncology until their condition has advanced beyond the help of all known medical recourse, and the pathology of the disease is anticipated to run its course. For this reason, the patient's life expectancy is limited. This shows in the number of deaths occurring under 30 days on the service. These patients were so deteriorated that death was already too close to be postponed. It will be noted that the period between 31 and 90 days equals two months, during which 49 of the patients survived; the mean average would be 28.5 patients per month this time, or 15.5 percent more patients survived during one month, after having survived the first month, than had survived the first month.

While most patients know of their condition by the time they are transferred to Oncology, there are some who, for some reason or other, are unaware of it. As shown by the table, the greatest number of patients expire during the first 30 days on the service. If these patients have had casework help previous to this, it may be hoped that they and their families are fairly well adjusted to the illness and its demands. If the social worker sees the patient and family for the first time on Oncology, those patients whose condition is terminally critical necessitate prompt attention which usually is in the realm of dealing with the realities.

Table 6

Number of admissions from date of entering oncology service

Admissions	No. Pts.	Percent
0	5	3%
1	59	38
2	52	33
3	25	17
4	7	4
5	1	1
6	1	1
7	0	
8	2	1
9	0	
10	1	1
11	1	1
Total	154	100%

The greatest number of patients expired after having from one to three admissions to the hospital for inpatient care after entering the Oncology service. One patient had eleven admissions, which was the greatest number of admissions for the base year. These figures are not significant without determining the contributing factors.

Table 7

Number of inpatient days after entering oncology service

Number of days	No. Pts.	Percent
Under 30 days	94	61%
31 — 60 days	38	24
61 — 90 days	9	6
91 — 120 days	3	2
Over 121 days	4	3
No in-patient days	6	4
Total	154	100%

It must be borne in mind that the number of inpatient days represents the total number of days spent in the hospital during the total time of patient's care on Oncology, and does not mean consecutive days. The greatest number of patients spent up to 60 days as inpatients. Of these patients (132), 94, or 71 percent spent less than 30 days as inpatients. The 38 patients who were hospitalized for between 31 and 60 days comprised 29 percent of this predominant group. The contributing factors would indicate the significance of this incidence.

Table 8

Patient's employment status

Status	No. Pts.	Percent
Unknown	3	2%
Wage-earner w/o dep.	18	12
Wage-earner w/dep.	49	32
Housewife or dep.	48	31
Retired w/o dep.	10	6
Retired w/dep.	18	12
Unemployed	8	5
Total	154	100%

The total number of patients having dependents at time of care on Oncology was 67, or 44 percent of total patients. The total number of patients without dependents was 28, or 18 percent. The total number of persons dependent upon someone else other than themselves was 48, or 31 percent. These included housewives, children, and other dependent persons. There were eight persons unemployed at the time they entered the service, comprising 5 percent of all persons.

These figures establish the patient's status economically, without which information the medical team could not function adequately, although this is of general consequence rather than specific. From this information other premises for direction may be made.

Of the resources available to the patient's use for medical expenses, 15, or 10 percent were used in combination with other resources. The greatest number of

Table 9

Source of patient's income while on oncology service

Source	No. Pts.	Percent
Unknown	11	7%
Personal resources	122	79
Relatives	16	10
Public Welfare	2	1
Disability insurance	18	12
Total	169	109%

patients financed their illness with their own personal resources.

This is a more specfic breakdown of resources, but the medical histories of the patients do not provide this information as such, nor do the fiscal records. The figures used for this table were gleaned from such other information that was acquired incidental to the medical record, hence there was inconsistency between the individual cases. It was assumed that 122 of the patients, or 79 percent, paid for their medical expenses from their own personal resources.

Table 10

Type of resources used to finance illness while on oncology

Source	No. Pts.	Percent
Unknown	14	9%
Blue Cross	115	75
Commercial insurance	8	6
Private insurance	11	7
County or state charity	12	8
Hospital charity	5	3
Personal resources	15	10
Total	180	118%

Of all sources used, 26, or 14 percent were used in combination with other resources. 75 percent of the patients owned Blue Cross insurance. The next highest source of resource was personal, at 10 percent. These figures are skewed because of lack of sufficient information.

That 115, or 75 percent of the patients used Blue Cross insurance for their medical expenses is important. In such a program as the one being described, it is important for the team to know how the patient's insurance operates. Admissions and lengths of stay may be regulated if necessary, to meet the benefit requirements. Knowing that frequent admissions may be necessary over a long period of time the staff can help the patient to keep the insurance in effect for future admissions by minimizing the lengths of stay. Into these pecuniary considerations are interjected the emotional factors. Emotions are as important for a patient's full recovery as are the services obtainable by money. If there can be a choice of hospitalization or home care, the emotional element is an important factor, and should be a major consideration, regardless of insurance benefits.

Ability to meet medical expenses is source for much anxiety for the patient and his family. Therefore, the medical team should be aware of the patient's resources, their worries, in order to plan accordingly.

Table 11

How patient was cared for outside of hospital while on oncology service

Type of care	No. Pts.	Percent
Unknown	21	14%
Lives alone	6	4
Family help in home	95	62
Hired help in home	5	3
Relatives or friends	19	12
Nursing home	6	4
Visiting Nurses Association	41	27
Other	1	1
Total	194	127%

A combination of outside services was used in 40 instances, or 27 percent. Most of the patients were cared for in their homes by their own families, and a large number of these had supplemental help from the Visiting Nurses Association. It is interesting to note that the number who went to a nursing home is the same as the number (6) who lived alone.

Since home care is urged for the Oncology patients, awareness of how this can be managed is of utmost importance. A discrepancy with this statement appears, in that the table shows 21 patients, or 14 percent of all patients, had no record of what their care outside the hospital was. It may be assumed that most of those patients were cared for in their homes, which would raise the figure of 95 patients, or 62 percent, of those helped in home to 116 patients, or 76 percent.

Table 12

Patient's performance status at time of entering oncology

Status	No. Pts.	Percent
Able/normal activities	30	19%
Unable to work	54	35
Unable to help self	69	45
Paraplegic	0	
Total	154	100%

Most people entering Oncology service were unable to carry on their normal activities.

This table alone does not hold much significance for this study. To be important, there should be a record of the number and degree of the patient's remissions.

Table 13

Agency help received by patient while on oncology service

Agency	No. Pts.	Percent
Social Service	37	24%
American Cancer Society	10	6
Visiting Nurses Association	41	27
Other	1	1
None	109	71
Total	198	129%

These agency services were used in combination in 44 instances, or 29 percent while 71 percent of the patients sought no agency help.

The figure shown on this table may not be entirely dependable, since the patient could have had services, and probably did, that were not recorded. However, services by the hospital's departments of Social Service and Public Health Liaison are quite apt to have been included with some degree of reliability. These were usually given to the patient concurrently.

Table 14

Type of service rendered by social service while patient was on oncology service

Type of Service	No. Pts.	Percent
Financial planning	22	59%
Discharge planning	14	38
Patient's emotional probs.	5	14
Family's emotional probs.	4	11
Environment manip.	18	49
Referral to other agency	0	
Other	0	
Total	63	171%

This table uses the number of patients helped by Social Service as its base, a total of 37 patients. These 37 patients used a total of 63 services offered, or 171 percent of total kinds of services. This indicates that 71 percent of the offered services were used in combination by some of the patients.

Financial planning, discharge planning, and environmental manipulation received the bulk of services rendered by Social Service. This is like measuring tangibles against intangibles, as supportive casework was not measured, but given.

MARLEX MESH — A NEW PLASTIC MESH FOR THE REPAIR OF HERNIA

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The introduction of new plastic materials has been one of the most fascinating developments of the past decade. The medical uses of these new plastic materials have been widespread. As each new plastic is introduced, its potential uses in the medical field are soon investigated. Some have physical qualities which lend themselves very readily to insertion into the body for various purposes. Of these, Dacron, Ivalon, Teflon and Polyethylene have become most useful. Polyethylene in the form of tubing has been widely used since its early introduction, and its many advantages over rubber tubing soon appreciated. A new Polyethylene plastic mesh named Marlex 50 was introduced several years ago in the hope that it would be useful for the repair of hernia.[1] A monofilament mesh, it has outstanding chemical resistance to acids and alkalis. It has a high tensile strength, creates very little foreign body reaction and is well tolerated in tissues.

ADVANTAGES OVER METAL MESH

This plastic material has many advantages over any type of metal since it is more pliable and readily inserted to any sized defect. It does not have the disadvantage of fragmenting or breaking up which the metal meshes do. It thus can be used in an inguinal area, or in any other area in the body, where it is subjected to considerable bending, without resulting in distress or discomfort to the patient. This plastic material is less affected by infection than are the metal types of prosthetics. Infection studies in animals showed that granulation tissue will grow through the mesh in the presence of purulent infection without slough of the graft or sinus formation.[1] A further significant advantage is that it is much more easily handled, and easier to work with in every way. These advantages make it seem likely that Marlex will completely replace types of metal mesh previously in use.

LABORATORY INVESTIGATIONS

This new plastic mesh had been previously tested.[2,3] However, we implanted it in dogs and guinea pigs, completely removing a segment of the abdominal wall and then using the Marlex mesh to bridge the gap. This material was left in place for six months and then the areas were examined. A rectangular area of 6 cm. x 8cms., of the rectus muscle and peritoneum which had been excised and the Marlex inserted to close this gap was completely firm and intact giving a normal appearing abdominal wall when later examined (Figure 1). In all cases, the wounds healed without infection and a very excellent support was obtained. Cross section and microscopic examination of the removed specimen showed that there was very little foreign body reaction to the material. It was well tolerated in the animal tissues. These favorable properties make this Marlex Mesh the best prosthesis for replacing tissue defects which we have yet encountered.

CLINICAL MATERIAL

The first operation in which Marlex mesh was used was done by one of us

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Figure 1

The appearance of the abdominal wall of a dog six months after the total thickness of the wall was replaced by marlex mesh.

(BEB) on 1/14/59. This was a large incisional hernia occuring through an old appendectomy scar. There had been perforation of the appendix with a lot of purulent drainage resulting in a large hernia at the location of the incision. There

was such loss of tissue that when the layers were developed at the time of the operation, they could not be satisfactorily approximated without tension. Relaxing incisions were used and the tissues could then be more satisfactorily approximated, however, a very weak area remained. A Marlex prosthesis 8 inches by 6 inches was sutured under the anetrior layer of the fascia, completely covering the weak area of the repair (Fig. 2). The patient's postoperative course was uneventful. The wound healed very well and has remained healed. The abdominal wall is strong and in excellent condition.

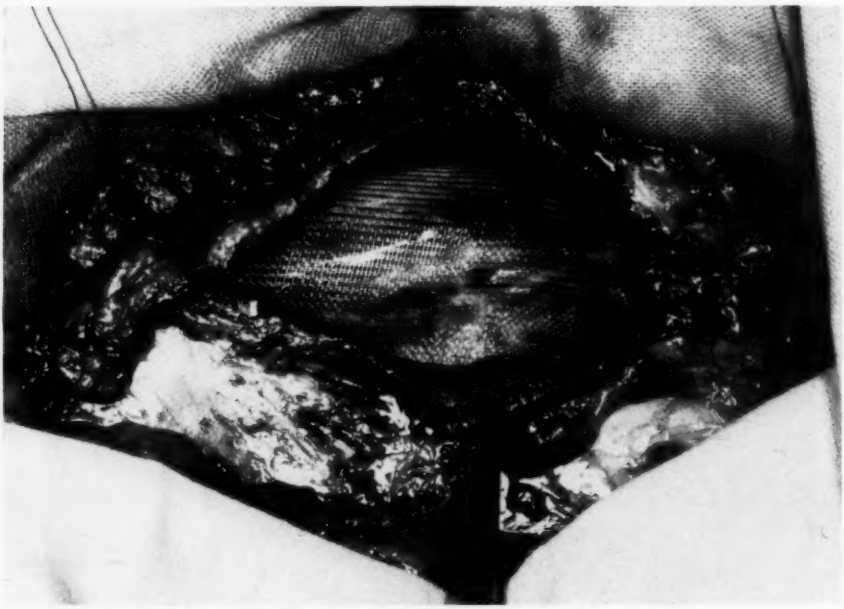

Figure 2

Marlex Mesh inserted between fascial layers of patient.

CONCLUSIONS

The unusual physical properties of Marlex — a polyethylene mesh — make it a very valuable plastic for surgical prosthesis. We have been well pleased with the results obtained with its use in the laboratory and in clinical practice as an adjunct in the repair of difficult herniae. Its advantages over metal meshes previously used make it likely to become the most popular material in its field.

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TREATMENT OF CONGESTIVE HEART FAILURE WITH 3-BENZYL DIHYDROFLUMETHIAZIDE: PRELIMINARY REPORT

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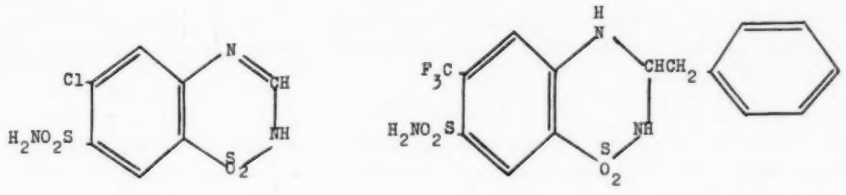
Since the introduction of chlorothiazide in 1957,[1] several analogues of the benzothiadiazine series have been made available for the treatment of edematous states, and most widely applied in the treatment of congestive heart failure. Hydrochlorothiazide, flumethiazide and hydroflumethiazide, in addition to the former, have all been reported to be potent oral diuretic agents.[2-4]

Toxicity to this group of drugs has been low, despite their wide clinical use. The most serious side effects are related to depletion of electrolytes, particularly of potassium and chloride. Efforts to develop more potent agents with fewer side effects, however, will undoubtedly continue.

A new substituted benzothiadiazine derivative, 3-benzyl dihydroflumethiazide, has recently been made available for clinical trial (Figure 1). Preliminary animal studies and clinical tests indicated that its diuretic activity was significantly greater than that of chlorothiazide and dihydroflumethiazide.[5]



Chlorothiazide 3- Benzyl Dihydroflumethiazide

Figure 1 Structural Formulae

METHOD

3-benzyl dihydroflumethiazide was administered to a group of 21 patients with congestive heart failure. The subjects were divided into three groups as determined by the severity of the congestive failure and response to previous diuretic therapy (Table 1). Grade I patients had mild to moderate degrees of congestive heart failure,

Table 1

Type of congestive heart failure of 21 patients

Etiology	Grade I	Grade II	GradeIII	Total
Arteriosclerotic	2	9	2	13
Rheumatic	0	6	0	6
Congenital	1	1	0	2
TOTAL	3	16	2	21

manifested by dyspnea, moist basilar rales and hepatic congestion. Grade II patients

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Drug material for this study was supplied by E. R. Squibb & Sons, Division of Olin Mathieson Chemical Corp., New Brunswick, N. J.

had severe degrees of heart failure with edema and/or ascites, while Grade III patients consisted of those who had become resistant or refractive to previous diuretic therapy.

Thirteen patients had arteriosclerotic heart disease, 6 had rheumatic heart disease and there were 2 cases of congenital heart disease. All patients were digitalized and maintained on 400 to 1600 mgm. sodium diets as indicated. The majority had received previous diuretic therapy, mercurials and/or one of the benzothiadiazine derivatives.

Seventeen patients were hospitalized and actively treated because of their decompensated status. A daily weight was obtained as well as regular blood counts, urinalyses and blood urea nitrogen determinations. Serum electrolytes were determined prior to and immediately after each period of diuretic administration. In 4 cases the drug was substituted for a previous diuretic agent as maintenance therapy in the out-patient clinic.

The drug was administered in a dosage of one 5 mgm. tablet two to three times daily for a period of two to three days, followed by a rest period of the same duration. In a few instances of severe congestive heart failure, the drug was given for a longer consecutive period. Patients previously treated with chlorothiazide or hydrochlorothiazide were given 5 mgm. of the new agent in place of 500 mgm. of the former or 50 mgm. of the latter. Ammonium chloride was given concurrently in about one-half of the cases while supplemental potassium salts were used in only a few instances.

RESULTS

Grade I. Two patients with arteriosclerotic heart disease and one with congenital heart disease (aortic stenosis) had early congestive heart failure. One had received no previous diuretic therapy. All had a good response with a weight loss of 2 to 7 pounds. No marked change in serum electrolytes was noted. One patient continued to have diuresis on the third day after the drug was discontinued, a phenomenon we have previously noted with hydrochlorothiazide, and described again in Case 2 below.

Grade II. Sixteen patients were classified as having Grade II congestive heart failure, 9 with arteriosclerotic heart disease, 6 with rheumatic heart disease and 1 with congenital heart disease (atrial septal defect). Of 12 hospitalized patients, all had a good diuresis with weight losses ranging from 4 to 25 pounds. Ten of these 12 had received prior therapy with mercurial or the benzothiadiazine diuretics and all responded equally well or better to 3-benzyl dihydroflumethiazide. No toxicity was noted and no severe electrolyte depletion occurred. All showed evidence of a mild hypochloremic alkalosis as noted with the prior thiazide derivatives.

Case 1. W. G. was a 48 year old man who had known rheumatic heart disease with aortic incompetency since the age of 18. Nine months prior to admission he developed atrial fibrillation and signs of congestive heart failure. Despite conversion of the arrhythmia on two occasions a sinus rhythm could not be maintained. He did well for a time on digitalis, a low sodium diet and intermittent administration of chlorothiazide and occasional injections of a mercurial diuretic.

He was admitted to the hospital on Sept. 2, 1959, because of increasingly severe exertional dyspnea, nocturnal dyspnea and orthopnea. The blood pressure was 132/62. There was atrial fibrillation at a rate of 84 per minute and aortic systolic and diastolic murmurs with an absent A2. There were medium moist rales in both lung bases and the liver edge was palpable 5 cm. below the costal margin and was tender.

He was continued on digitoxin 0.1 mgm. daily and a 400 mgm. sodium diet. On the first day of administration of 3-benzyl dihydroflumethiazide he lost 10 pounds and felt much improved. He lost a total of 20 pounds during the 8 days of intermittent administration of the drug (Figure 2), and the congestive failure was completely controlled. Slight hypochloremic alkalosis was the only change in electrolytes noted despite the fact that no supplementary chloride or potassium was given.

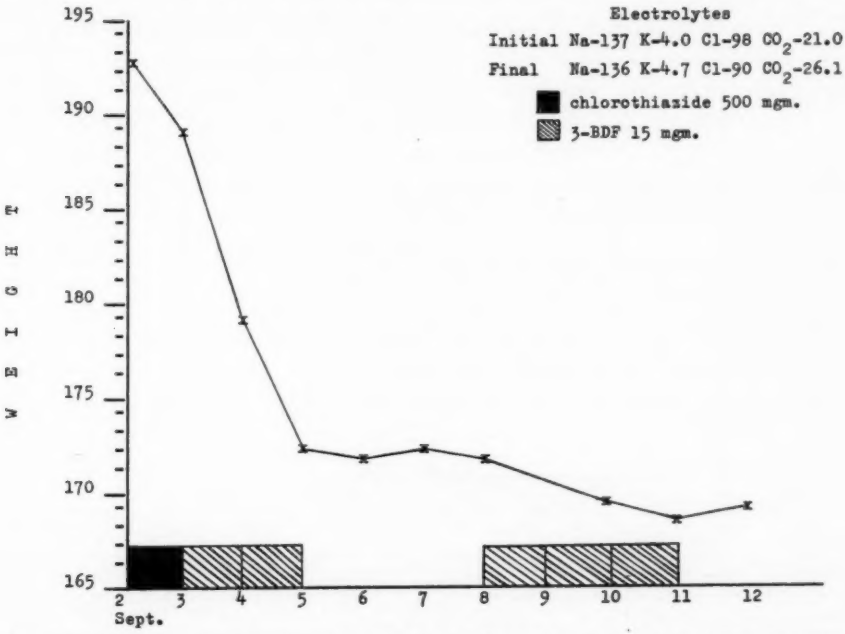

Figure II. Weight loss and electrolyte change in W. G. (Case 1) on 3- benzyl dihydroflumethiazide. Complete control of congestive failure in 10 days.

One Grade II patient showed the continued diuresis following cessation of drug administration referred to above and warrants a brief case report.

Case 2. C. F. was a 54 year old Negro male who had been treated at this hospital in 1953 for an acute anterior myocardial infarction. In January 1956 he first developed congestive heart failure and in the ensuing years was hospitalized on several occasions for the treatment of exacerbations of chronic congestive heart failure. He was unable to work since October 1957.

He was re-admitted on July 5, 1959, because of an increase in dyspnea, ankle

edema and loss of appetite. The heart was grossly enlarged and there was a gallop rhythm with frequent premature systoles. The liver edge was palpable 6 cm. below the costal margin and tender. There were bilateral moist basilar rales and 3+ pretibial pitting edema.

Digitalis and a 400 mgm. sodium diet were continued. After four days of stable weight, 3-benzyl dihydroflumethiazide was given in a dosage of 5 mgm. three times daily. A prompt diuresis resulted. (Figure 3) After 7 consecutive days of drug administration it was discontinued, but diuresis continued and he lost an additional 11 pounds of weight in the next 6 days without any other change in therapy.

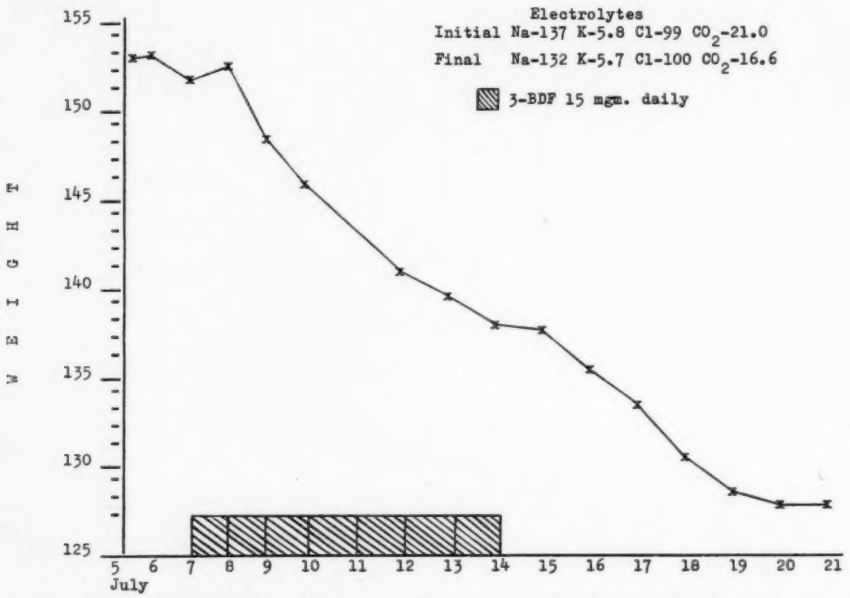

Figure III. Weight loss and electrolyte change in C. E. (Case 2) with 3- benzyl dihydroflumethiazide. Note continued diuresis following cessation of drug. Congestive failure completely controlled.

Four patients with Grade II congestive heart failure were treated in the outpatient department. Two patients with rheumatic heart disease were well controlled on chlorothiazide and continued to do equally well when given the new maintenance diuretic. Two patients with arteriosclerotic heart disease and near the terminal stage of their disease were poorly controlled on a maintenance dose of chlorothiazide and intermittent injections of mercurial diuretics. No improvement was noted when 3-benzyl dihydroflumethiazide was substituted for the chlorothiazide.

Grade III. Two patients with arteriosclerotic heart disease and severe advanced congestive heart failure had become refractive to mercurial diuretics, chlorothiazide and hydrochlorothiazide. The serum electrolyte patterns were within the normal range. Neither showed any response to 3-benzyl dihydroflumethiazide.

COMMENT

The thiazide derivatives produce diuresis as a result of blockage of the tubular transport mechanisms involved in the reabsorption of sodium, chloride, and, to a lesser degree, of potassium and bicarbonate. The electrolyte excretion patterns are basically similar, though definite differences have been noted.[4] Beyer and Baer are of the opinion that this does not necessarily indicate a difference in pharmacologic action, but is more likely related to differences in the back diffusion of chloride and bicarbonate secondary to differences in distribution of the drug.[6]

3-benzyl dihydroflumethiazide would seem to share this same mechanism of action. On a milligram for milligram basis, however, it is a more potent agent than chlorothiazide or hydrochlorothiazide, being approximately 100 times more potent than the former and 10 times more potent than the latter.

Mild hypochloremia was noted in all cases in which diuretic responses were obtained. This was easily corrected by the administration of ammonium chloride. No significant reduction in the levels of serum sodium or potassium was observed. No change was noted in the blood count, urinalysis or BUN of any case.

3-benzyl dihydroflumethiazide was well tolerated by all patients in this series. No side effects were noted. A low incidence of nausea, vomiting and weakness has been reported previously with chlorothiazide and hydrochlorothiazide.

These results indicate that 3-benzyl dihydroflumethiazide is a potent oral diuretic agent. A decreased incidence of side effects, if substantiated by further study, would be a decided advantage over previous thiazide derivatives. Further investigation may also indicate that there is less of a tendency to depletion of sodium and potassium, though these should be watched for in long continued use of this agent as with the other thiazide derivatives. This is particularly true of the patient with advanced cardiac or hepatic disease.

SUMMARY

A new benzothiadiazine derivative, 3-benzyl dihydroflumethiazide, was administered to a group of 21 patients with varying degrees of congestive heart failure. Results of this preliminary study indicate that it is an active diuretic agent approximately 100 times more potent than chlorothiazide. No toxicity or serious electrolyte disturbances were noted.

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OBSTETRICAL MANAGEMENT OF THE PREGNANT CARDIAC PATIENT

GEORGE E. LACROIX, M.D.,* AND ELI J. IGNA, M.D.*

The gradual ebb of toxemia, infection, and subsequently hemorrhage, as the predominant causes of maternal mortality has placed cardiac disease in a prominent position. It acounts for about 25% of maternal mortality. Further decrease of this mortality rate depends upon present and future clarification of normal and abnormal cardiovascular and respiratory physiology during pregnancy. Such knowledge makes successful management of both the pregnancy and cardiac disease more feasible with the outcome a dual reward of a living mother and a healthy child.

The make-up of an obstetrical clinic's cardiac population differs from area to area, but in general averages 80 to 85% rheumatic heart disease with the sole or predominent lesion mitral stenosis in 70%. The remainder consists of congenital cardiac defects such as patent ductus arteriosis, coarctation of the aorta, tetralogy of Fallot etc., the rarer acquired cardiac diseases as luetic, thyrotoxic, and hypertensive cardiovascular disease, myocardial insufficiency and coronary occlusion.

PHYSIOLOGY:

Striking changes are evident in many organ systems during pregnancy designed to accommodate both maternal and fetal metabolic needs. Although much valuable investigative work has been done in this field, it remains a fertile area for additional clinical research.

Changes in the cardiovascular system are predictable and measurable, and in many ways, resemble an arteriovenous shunt. The cardiac output, heart rate, and blood volume increase during normal pregnancy becoming significantly elevated in the second trimester and reach a peak six to eight weeks before term. Thereafter they drop gradually with the optimal levels at term, thereby providing an additional cardiac reserve for stresses of parturition. Cardiac output at its peak increases 30 to 50%. Oxygen consumption increases somewhat less, approximately 20%, reaching its highest four to six weeks before term. The red cell mass increases steadily, but proportionately less than plasma volume, resulting in decreased hemoglobin and hematocrit levels which are most depressed at the peak of the cardiovascular load. Total body fluid increases steadily to term.

Pulmonary changes are likewise significant. The increased ventilation of the pulmonary tree facilitates excretion of fetal and maternal metabolic wastes, particularly carbon dioxide. The vital capacity generally increases, but most important, does not decrease during pregnancy. This occurs despite a presumed interference with respiration by the enlarging abdominal tumor. Many feel this test is particularly useful in detecting early edema and insipient cardiac failure before other clinical signs become evident.

During labor, oxygen consumption, heart rate, and cardiac output increase somewhat proportionately to the severity and number of uterine contractions. The

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Valsalva Maneuver comes into play during the "bearing down" and expulsive phases of the second stage, but cardiac output itself does not increase concomitantly.

Delivery causes a sudden change in hemodynamics. The release of pressure obstructing the return of venous blood from the legs, as well as the release of upwards of 500 cc. of blood from the uterine veins and sinuses into the general circulation may effect a sudden heavy burden upon the heart.

Following an immediate partial readjustment within 24 hours after delivery, there is a gradual return to the "normal" non-pregnant status, which is generally complete by four to six weeks.

These alterations in pregnancy, labor, and delivery, are usually well tolerated by the healthy patient, but not so by the patient with mitral stenosis. In this condition, the stenotic mitral valve impedes left ventricular filling during diastole. The pressure in the left atrium is secondarily increased with retrograde extension of this pressure into the pulmonary venous and capillary beds. Thus the additional load as imposed by a normal pregnancy with increases of heart rate, cardiac output, or total circulatory blood volume can further accentuate this defect, and automatically places the patient with mitral stenosis closer to pulmonary edema and failure. If, in addition, other stresses are added that shorten diastole or increase these cardiovascular changes, an already dangerous situation may be compounded with fatal outcome for the mother and the fetus.

DIAGNOSIS AND CLASSIFICATION:

Approximately 3 to 4% of an obstetrical clinic's population will have significant cardiac disease. About half of these will be unaware of any cardiac problem. This emphasizes the importance of the initial history and physical examination that is performed by the obstetrician. Both definite and potential disease must be evaluated by the cardiologist. Joint cooperation between the obstetrical and medical departments has been shown to improve dramatically the maternal and fetal salvage.

Cardiac evaluation and diagnosis must be established. Early evaluation will generally indicate which patients may transcend pregnancy satisfactorily, which may not, and those who are liable to difficulties. Such procedures as cardiac catheterization, chest x-ray, and fluoroscopy should be done where indicated regardless of the duration of gestation. The resulting functional and organic disease classification will determine, in effect, the care and stringency to be followed by both patient and physician. Functional capacity is, in general, the most important clinical guide to prognosis during pregnancy.

MANAGEMENT:

Careful present day medical management can carry most patients with mitral stenosis through pregnancy successfully. Sterilization is seldom indicated or advocated in pure mitral stenosis. If interruption becomes necessary, the earlier the procedure is done the less the risk to the patient. Cardiac surgery has been shown to be preferred when feasible over interruption. The status of the stenotic valves and the change of function following mitral commissurotomy offer a guide to imme-

diate prognosis. When possible, mitral comissurotomy should be performed between pregnancies.

Each case of mitral stenosis must be individualized both as to diagnosis and management, though general principles do apply. In most of these patients, it is the pregnancy, and not the labor and delivery that decides the fate of the patient. The cardiac patient with minimal disease and minimal functional impairment needs little aid beyond adequate counciling, routine prenatal visits, and the usual cardiac evaluation. Those with significant disease with either minimal or severe functional impairment will require frequent visits to the obstetrician and cardiologist as well as intensive counciling as regards medical and personal care, and family management during the pregnancy.

Primarily, attention is directed towards control of the blood volume, cardiac rate and output, as these effect directly the incidence of cardiac decompensation. A past history of cardiac failure may predispose the patient to more difficulty during the ensuing pregnancy, but regardless of previous history, failure can occur in any patient at any time during pregnancy. The greatest hazzard occurs approximately eight to ten weeks prior to term and immediately following delivery.

The cardiac reserve must be maintained, not necessarily at the optimal condition, but with a sufficient margin for safety. The patient's family responsibility including physical and emotional stresses must be minimized. To help attain this, aid may be obtained through the patient's family, Nursing or Social Services, and Cardiac Rehabilitation Centers.

Specific measures include dietary restrictions. Limitation of salt both in diet and in medication is the most potent tool for control of blood volume and edema. Diuretics also aid in their control. Adequate protein intake helps maintain the proper homeostatic and osmotic balance. Excessive weight gain must be avoided.

Rest is of prime importance. The patient should receive adequate nocturnal rest, and this may be accomplished with sedatives if necessary. Additional rest periods are indicated by her daily activities. Total bed rest may be necessary in some cases during the entire pregnancy.

Infections and anemia must be treated vigorously. Respiratory infections and severe anemia necessitate hospitalization for their active control as they may precipitate acute cardiac failure. Parenteral iron or transfusions with whole blood or packed cells must be resorted to when oral iron is ineffective. Decompensation during pregnancy is treated essentially as in the non-pregnant patient.

Admission to the hospital at 37 to 38 weeks of pregnancy may be valuable for rest and evaluation prior to delivery. Elective induction of labor is generally contraindicated as the optimal time for cardiac function and peak reserve is not reached until term. Should premature rupture of the membranes occur at term, Pitocin induction may be initiated after a preliminary rest period. Labor should be permitted to progress normally, but the second stage should be shortened by the judicious use of forceps. The use of analgesics as Demerol, and sedatives may be used in moderation, but Scopalomine and other antivagal stimulants must be used sparingly and in

minimal doses, because of their effect upon the pulse rate. Pudendal block, caudal, and ether anesthesia are listed in order of preference. Excessive blood loss and shock must be prevented. Parenteral fluids and blood must be given cautiously.

Placing the legs in stirrups prior to delivery decreases a portion of the sudden flooding of the cardiovascular system. Should cesarean section be done, rotating tourniquets to three of the four extremities may permit more gradual readjustment of the circulating blood volume. The postpartum stay should be of sufficient duration to guard against complications of infection, anemia etc. During this period of time, the patient can be given further instructions as regards to care of her newborn infant, household duties and convalescence. Nursing is generally contraindicated in the severe cardiac.

Once convalescence has occurred, pregnancy does not seem to accelerate the course of heart disease.

CONCLUSIONS:

1. Present day management of the patient with mitral stenosis generally permits satisfactory conduct and termination of pregnancy.
2. Early evaluation is necessary to determine the course to be followed, i. e., interruption, sterilization, or cardiac surgery. Sterilization for mitral stenosis now is seldom indicated.
3. Functional capacity is in general the most important clinical guide to prognosis during pregnancy.
4. Decompensation during pregnancy is essentially treated as in the non-pregnant patient.
5. Pregnancy is best terminated by labor and elective forceps delivery. Cesarean section is utilized only for obstetrical reasons.

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A REVIEW OF PSYCHOPHARMACOLOGIC DRUGS

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Almost every week a new drug is marketed which is aimed at altering psychic behavior. This review is an attempt to group and to clarify the actions of this growing multitude. In many cases the actions of members of a group are essentially identical and the choice will be determined by which sales representative visited you or by a chance initial favorable response to one of them. There are however some advantages which may prove helpful in solving specific problems. The following is a general outline of current drugs, their indications, dosage, and side effects.

I. Psychic inhibitors

A. Sedatives (in moderate doses) and Hypnotics (in larger doses) — These reduce the activity of the cortex primarily although in large doses the functions of other portions of the nervous system may be reduced. No effect on delusions or other psychotic processes.

1. Barbiturates — Although this is a large group, many doctors do not take advantage of their varied durations of action. Short acting compounds given to older persons may produce delirium whereas the longer acting ones may not. A person having trouble falling asleep will benefit more from a short acting drug which will not impair his awareness upon arising while the person who can not remain asleep may require a longer acting compound. If given for pain without analgetics in addition, these may produce delirium. The prolonged adminstration of as little as 4 grains of sodium amytal daily may produce habituation with a withdrawal syndrome including convulsions.
2. Bromides — skin reactions and toxic psychoses may result.
3. Chloral hydrate — usually well tolerated by even the aged. 0.5-1.0 gm. available in capsules and liquid.
4. Paraldehyde — an ideal potent drug except for taste and odor. 5-10 cc. This objection can be reduced by taking in iced fruit juice. Paral (Fellows) 1.0 gm. capsules are also available.
5. Doriden (Ciba) 250 mg t.i.d. for sedation, 500 mgm, h.s. for sleep.
6. Noludar (Roche) 50 mg for sedation, 200 mg for sleep. Similar to pentobarbital.
7. Carbital (Parke-Davis) 1 capsule for sleep.
8. Valmid (Lilly) 500 mg; very rapid short action; for sleep.
9. Lotusate (Winthrop-Stearns) 50 mg t.i.d.
10. Placidyl (Abbott) 100 mg t.i.d. for sedation; 500 mg for sleep.
11. Quiactin (Merrell) 400 mg q.i.d. for sedation.
12. Softran (Stuart) 50 mgm t.i.d.
13. Suvren (Ayerst) 100 mg t.i.d.; also spasmolytic.
14. Scopolamine.

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15. Narcotics — use only when severe pain is a factor.

16. Meprobamate 400 mg q.i.d. This is basically a sedative although it also has a definite effect upon the peripheral neuromuscular system producing muscle relaxation; actually this may be its primary action. Conditioned responses are blocked only at neurotoxic levels. Like barbiturates it is habituating and withdrawal syndromes may follow its discontinuance. Aplastic anemia and three deaths have been reported. It is a poor drug for producing sleep but is of special benefit in conditions where muscle relaxation as well as sedation is desired as in wry neck, tension headache, neuromyositis, etc.

B. Neuroleptics — these block conditioned and avoidance responses and are especially good for reducing aggressivity. In moderate doses cortical activity and peripheral actions are not impaired but persons working around moving machinery or driving should be cautioned and watched carefully initially as some persons are affected. Barbiturates and alcohol are potentiated. This must be considered in anaesthesia and in the patient who might have his usual few drinks and attempt to drive.

1. Rauwolfia compounds — these act by liberating serotonin and biologically active catecholamines from various body cells whereupon they are destroyed by oxidases, especially monoamine oxidase. Adenosine triphosphate levels are also altered. These drugs act more slowly than phenothiazines and are more likely to produce parkinsonism, asthenia, depressions so are not widely used now.

2. Phenothiazines — these may act by interfering with the action of nor-epinephrine in the brain.

Trade name	Manufacturer	Chemical name	Comparable Dose
Compazine	S K F	prochlorperazine	10 mg
Dartal	Searle	thiopropazate	10
Mellaril	Sandoz	thiodiazine	25
Pacatal	Warner	mepazine	50
Permitil	White	triflurmethyl phenazine	0.25
Prolixin	Squibb	fluphenazine	1
Sparine	Wyeth	promazine	50
Stelazine	S K F	trifluoperazine	2
Tentone	Lederle	methoxypromazine	25
Thorazine	S K F	chlorpromazine	25
Trilafon	Schering	perphenazine	4
Vesprin	Squibb	triflupromazine	10

Indications — Hyperactivity, panic, agitation, assaultiveness, destructiveness, obsessions and compulsions (but to a lesser degree), acting out especially when it is interfering with psychotherapy, and to reduce the awareness of pain when symptoms are physically painful. Schizophrenia may possibly be associated with excessive transamination in which case rauwolfia and phenothiazines would be chemically indicated. In the acute forms without paranoia or profound dissociation

phenothiazines produce a cure of better quality and duration than does insulin coma. The paranoid type does better on phenothiazines than with either EST or insulin. The catatonic form does better with EST. The chronic form does as well on phenothiazines as any other therapy. Improvements seen with phenothiazines are of better quality than spontaneous cures. Initially some patients feel a void where the "voices" had counselled or governed them and experience difficulty at first in making their own decisions. Catatonic stupor and excitement are usually relieved. "Word salad" disappears and meaningful speech becomes possible.

The apperception of incoming stimuli both from within and from the environment is apparently reduced. Defenses and inhibitions may then be reduced as that against which they were defending is perceived as less threatening. Perhaps because the energies of instinctual drives is lessened the superego is not as rigid in denouncing them. Secondary delusions, obsessions, and compulsions become less imperative. The patient begins to feel less fearsome and less fearful both of himself and of others. Innate energies are released for further reorganization and reality testing and the personality undergoes progressive psychologic changes on the basis of more successful living. This may be hastened by psychotherapy. As the patient's behavior toward those about him improves, they will become more friendly toward him thus creating an improved and more gratifying environment.

In neurotics the dulling and stabilization of the autonomic system's functions reduces the physical complaints so that the patient can better see beyond them and concentrate on psychotherapy. The phenothiazines are often helpful in this without depressing cortical activity as much as the sedative group. Vague, generally uncomfortable, free-floating anxiety is not particularly relieved by any drug. The administration of any drug tends to increase the positive transference toward the doctor. This plus the attitude of the dispensing physician may produce powerful placebo effects of which you must be constantly cognizant. If the patient has no insight into the fact that psychologic factors are creating the symptoms and if you relieve the symptoms with drugs, it is possible that he may no longer desire to do anything about the cause but merely continue to demand the drugs. This is usually undesirable although in some individuals psychotherapy may not be feasible and also spontaneous cures under drugs alone are not unknown. Pathogenic drives are more readily affected than normal activities. However, if, as in character disorders, no such sharp distinction exists, an effective dose will likewise obtund normal functioning. In these only long term psychotherapy is indicated.

Complications with phenothiazines — The incidence of side effects is roughly proportional to the dosage but some individuals may react

to even small doses. These reactions usually appear within the first two weeks so the patient should be observed carefully during that period. It is probably good practice to check the white blood count at the end of that period. The most common complication is the development of a Parkinson-like syndrome. Both this and akathisia respond well to a reduction in the dose plus one of the anti-Parkinson drugs (Artane, Cogentin, Kemadrin). Akathisia consists of motor restlessness, inner sensations of jitteriness, and restless feelings in the legs. This is difficult to distinguish from the symptom for which you may be giving the drug and, unles you are alert for its occurence, you may increase the dosage and only aggravate the situation. All of the phenothiazines may cause a toxic hepatitis with jaundice although this is less frequent in the newer compounds. Skin rashes may occur not only from consuming the drug but from handling it especially the injectionable solutions. Other side effects may be dry mouth, drowsiness, hypotension, dyskinetic spasms and movements, fibrillary twitchings, and agranulocytosis. Should any hypotension be prolonged intravenous nor-adrenalin is indicated.

Symptoms in psychiatry are the patient's deviant expressions of his inability to face himself and his inner impulses. The alteration or control of these symptoms by a drug may be experienced by the patient as either beneficial or undesirable. This is determined to a large degree by the attitudes of the doctors, nurses, and others around him. Some may see the doctor, hospital, and the medications as part and parcel of a threatening situation against which they must muster every defense. The administration of drugs may thus be followed by more disturbed paradoxical behavior sometimes similar to akathisia; this however is not relieved by anti-parkinson drugs.

3. Diphenyl methane derivatives.

   a. Hydroxyzines
      (1) Atarax (Roerig) 25 mg t.i.d.
      (2) Vistaril (Pfizer) 25 mg t.i.d.

   b. Benactyzine of Suavitil (Merck) 1 mg t.i.d.

   c. Azacyclonol of Frenquel (Merrell) 100 mg t.i.d.

   These compounds are closely related to antihistamines and perhaps act by blocking some of the actions of serotonin. They are considerably weaker than phenothiazines but have somewhat similar indications.

II. Psychic activators

A. Stimulants — enhance conditioned avoidance behavior and arousal. These may be helpful for moderate asthenia, tiredness, or depression but a tolerance tends to develop quickly.

   1. Amphetamines - potent

2. Meratran (pipradrol) Merrell 2.5 mg b.i.d. - milder
3. Ritalin (phenidylate) Ciba 5 mg t.i.d. - milder

B. Energizers

1. Hydrazines — The current theory is that these act by preventing the destruction of serotonin and catecholamines by mono-amine oxidase however there are some doubts now that this completely and accurately explains the action. Since depression is postulated to be related to excessive oxidative deamination, this group of drugs was tested for anti-depressive action and has proven to be helpful in many cases. The action however is not dramatic and may require as long as a month. If the depression is not severe or if EST is contraindicated in severe depressions, these drugs are useful. In severe depressions, however, the danger of suicide often makes the more rapid treatment by EST preferred. Hypotension, constipation, jitteriness, and jaundice may occur.

a. Marsilid	iproniazid	Roche	25-50 mg tid
b. Marplan	benzyl hydrazine	Roche	10 mg tid
c. Nardil	phenethyl hydrazine	Warner	15 mg tid
d. Niamid	a complex hydrazine	Pfizer	25 mg tid
e. Catron	phenylisoproply hydrazine	Lakeside	3 mg tid

2. Tofranil - dibenzephine - Geigy 25-50 mg q.i.d.
   The action of this compound is not understood but empirically it has proven useful in combating depressions. Excessive sweating, dry mouth, and jitteriness may occur.
3. Deaner - diethylamino ethanol Riker 50 mg t.i.d.
   The action of this drug is much weaker than those above and is based upon the postulated conversion of the drug into acetyl choline which passes through the blood-brain barrier.

III. Psychomimetics or Dysleptics

This group consists of a number of compounds containing an indole nucleus such as lysergic acid diethylamide (LSD) and mescaline. Their effect may be through interfering with serotonin metabolism or other brain metabolic functions especially with carbohydrates. Their use thus far has been limited to experimental studies of the psychic and biochemical changes induced.

IV. Placebos

This group of "drugs" is probably the most neglected of all although repeated studies have shown that 25-35% of subjects reported definite improvement; some even developed remarkable "side effects". If the physician is able to afford his patient relief without introducing any potent and possibly harmful drug into his system, is he not to be more highly commended? This also helps prevent over-enthusiastic claims for a drug when the favorable results are more closely related to the doctor's enthusiastic approach to the patient.

BRONCHOPULMONARY MYCOSIS: A 20 YEAR STUDY OF SIBLINGS

BRENTON M. HAMIL, M.D.*[1,2]

W. R. EYLER, M.D.,** J. W. REBUCK, M.D.,*** AND G. A. LOGRIPPO, M.D.***

Throughout a period of twenty years, records have been accumulated of the acute onset and progress of bronchopulmonary mycosis in four siblings and their mother, with recovery of all the children, supervention of a fatal accident to the mother and the subsequent death of a fifth sibling, possibly due to the presence of the disease.[1] The five children had been under school health observation and were in good health prior to the onset of their illness. The sibling who died of what was diagnosed "atypical pneumonia with relapse" in another community at a later date was observed for only a short time following the onset of acute illness in the other four siblings and the mother. He lived in comparable environment, however, and no autopsy was done. The mother was observed for about one year and later was killed accidentally and autopsy was not possible. The four sibling children who were seen from the time of the acute onset of their illness were treated periodically in the hospital and through outpatient service over a period of four years. The treatment used which was considered to be the most effective in the accomplishment of healing was iodides which were used in large doses; potassium iodide by mouth, sodium iodide by vein and ethyl iodide by inhalation.

Both Candida albicans (Monilia Pinoyi) and Aspergillus niger were found repeatedly in all sputa and Candida albicans was grown from material taken from far down the main bronchus by bronchoscope in two patients and Aspergillus niger from the other two. The symptoms and lesions were similar in all and the cause was thought to be a mixed infection in all. Terminal treatment in three patients consisted of autogenous vaccine with Aspergillus niger — (Patient W.C.) and Candida albicans — (Patient P.C.) given in increasing dosage weekly for 50 weeks. This was begun in the third year of the illness, following cessation of Iodide therapy.

The source of the infection was determined likely to be the feathers in new feather beds which the patients slept between at the time of the acute onset of illness. These had been made from chicken feathers bought from a neighbor farmer who had killed his entire flock for market because of an illness which had plagued them. Other sources were possible in their environment but this seemed to be the most likely. Cultures of the fungi were obtained from samples of these feathers together with a variety of other fungi and yeasts. The four patients have been free of pulmonary or general symptoms since this time and have led normal, useful and productive lives. Periodic information has been obtained from all throughout a

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Scientific exhibit prepared under the direction of Mr. T. Stebbins, Dept. of Medical Illustration and Mr. J. Kroll, Dept. of Photography, Henry Ford Hospital. Presented at the 108th Annual Meeting, American Medical Association, Atlantic City, June 8-12, 1959 and at the IX International Congress of Paediatrics, Montreal, Canada, July 18-25, 1959.

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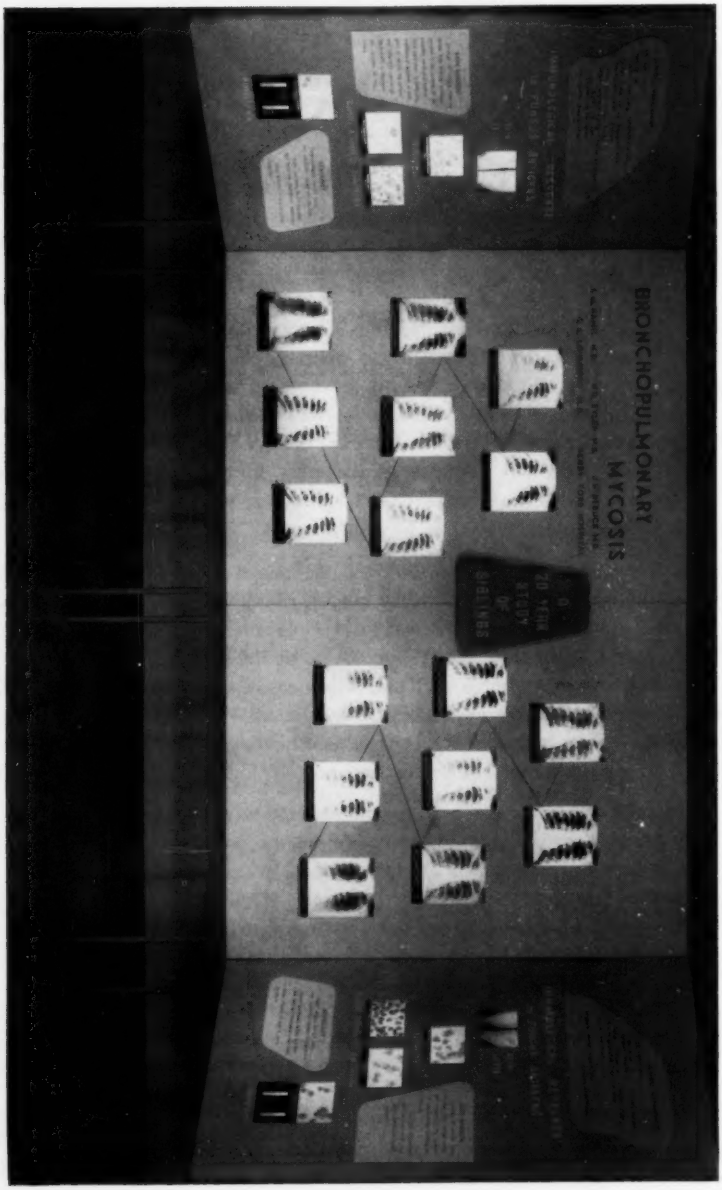

Figure. 1. Scientic Exhibit

period of 20 years. Three of them have had periodic roentgenograms of the chest annually or more often during this time. There have been no significant illnesses, no symptoms referable to the lungs, all are married and three have two or more normal, healthy children. One patient developed a partial transverse myelitis during the latter part of treatment at which time an organism identified as Candida albicans was obtained from the spinal fluid. No other complication has occurred.

All four patients showed a cross-reaction to application of a variety of fungus antigens early in the subacute course of their illness. Their sera showed a moderately positive agglutination titre to the autogenous Candida albicans (P.C) and autogenous Aspergillus niger (W.C.).

The patient who had the greatest extent of lung lesions and who developed partial transverse myelitis during the course of her treatment was ambulatory and had inadequate supervision of therapy for *2 years* before satisfactory hospital controlled intensive treatment was started. This is in contrast to the treatment which was received by the three siblings whose controlled therapy began *2 months* after the onset of illness. This patient did not have the course of autogenous vaccine desensitization because of the ocurrence of her partial transverse myelitis near the termination of drug therapy. Her present hypersensitivity is marked.

SUMMARY OF COURSE

Representative Siblings with Variation of Clinical Management

Case: J.C. (F. age 15 years at onset of illness) — Severe "flu" type symptoms 1-20-38 to 2-20-38; fever, chills, general malaise, prostration; relapse March 7, 1938 with continued fever, malaise, sweating, cough with gruel-like, sweetish, blood-streaked sputum, substernal pain and much prostration. Hospitalized 3-23-38 for intensive treatment program. Three siblings and the mother similarly, but less severely ill, and a brother had no symptoms, and chest x-ray negative. He developed atypical pneumonia 20 months later and expired in a relapse in his local hospital, having had same exposure to fungi. Aspergillus niger cultured from the hyperemic friable bronchial mucosa of J.C. and sibling W.C. Candida albicans cultured from white plaques on the bronchial mucosa of P.C. and sibling A.C. These organisms, together with other fungi, were grown from samples of feathers taken from newly made feather beds which were slept between. Mantoux O.T. and P.P.D. continously negative. Early response result of early intensive treatment with iodides. Autogenous vaccine used for attempt at desensitization at end of iodide therapy in this patient and two siblings hospitalized early. 50 weekly injections in gradually increased dosages.

Case: P.C. (F. age 12 years at onset of illness). Onset of symptoms almost simultaneously with three siblings and mother (Jan.-Feb. 1938). Remained ambulatory under potassium iodide medication at home. First hospital adm. 5-10-40 for intensive therapy 28 months after onset. Course of illness more protracted than of siblings who were hospitalized early. Developed partial transverse myelitis, upper lumbar cord (6-14-41). Candida albicans was found in one Sp.F. culture. This fungus was cultured from white plaques in bronchi (1-4-41) [also from bronchi of one sibling (A.C.)] [Aspergillus niger cultured from friable hyperemic mucosa of bronchi of siblings J.C. and W.C.].

Attempt at desensitization (6-20-41) with autogenous vaccines made from these organisms, consisting of 50 weekly injections in gradually increased dosages given to other three siblings, but not given to this patient. Mantoux O.T. and P.P.D. negative throughout observation for twelve years. Reaction to P.P.D. now positive. Delayed reaction to histoplasmin marked at this time. Protracted more severe course result of late intensive treatment with iodides. More antigen sensitivity possibly due to less heterologous neutralizing antibody because of no vaccine desensitization.

DIAGNOSIS AND CLINICAL MANAGEMENT*

The following significant factors have been considered to be important in the diagnosis and treatment of these patients. Other drugs were used for short periods but intensive therapy with iodides was the most significant. The only untoward reaction from the massive doses of iodides was the occurrence of symptoms of hyperthyroidism in one patient which soon disappeared when the drug was temporarily stopped.

Diagnostic Criteria

1. History of onset.
2. Initial cough.
3. Substernal pain.
4. Scant sputa.
   gruel-like
   blood tinged
   sweet-yeasty odor
5. Few or no ausculatory findings.
6. Roentgenographic appearance of lungs.
7. Negative tuberculin test.
8. Bronchoscope culture.
9. Intradermal hypersensitivity to fungus antigens.
10. C.F. Serology if suitable material is available.

Treatment

1. Adequate and prolonged rest.
2. Good diet high in protein and iron.
3. Adequate Iodide therapy Sat. Sol. K.I. 5cc to 20cc daily.
   10% Sod. Iodide I.V. 100cc daily.
   Ethyl Iodide by inhalation 4cc. q. 2-3days.
4. Expectorant as desired.
5. Periodic CBC and Sed. rate to detect exacerbation.
6. Occupational therapy and other supportive measures.
7. Protection from secondary complications.
8. Long-term follow-up for observation.
9. Avoidance of reinfection.
10. Vaccine therapy at termination of roentgen healing.

IMMUNOLOGICAL RESPONSE TO FUNGUS ANTIGENS

Cytology of Exudate After Application of Antigens

(Skin Window Technique)

In general the presence of antibody (hypersensitivity reaction) is reflected by the degree of lymphocyte response after application of the antigen to the scarified area. If there is little or no antibody present, as in the coccidioidin test, the exudative response for the first 12 hours is dominated by neutrophils, following which macrophages become the dominant type. In contrast, when there is a high degree of hypersensitivity or in other words a high titre of antibody present, the lymphocytes begin to predominate in the first 12 hours. This is shown in the cytological response for the two pathogens, Candida albicans and Aspergillus niger, and also to a less extent for the histoplasmin reaction. (Fig. 2-9)

*All pertinent data and information collected during the course of management of these patients are given in this reference.[1]

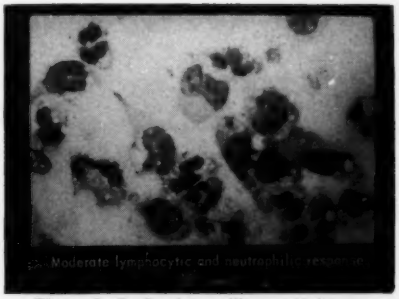

Figure 2. P. C.: Aspergillus — 10 hours

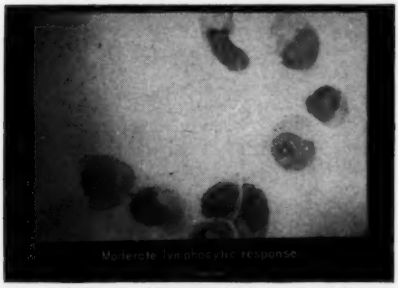

Figure 3. P. C.: Candida albicans — 10 hours

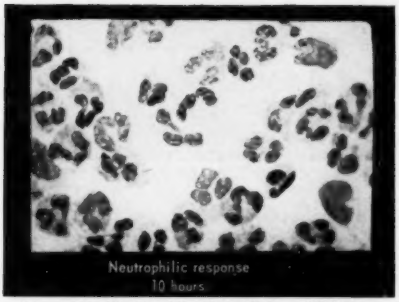

Figure 4. P. C.: Coccidioidin — 10 hours

Figure 5. P. C.: Histoplasmin — 10 hours

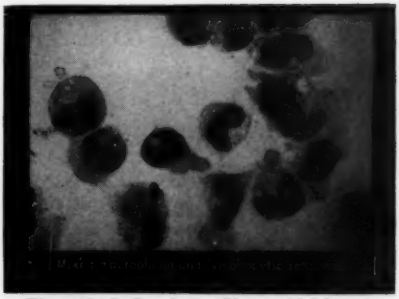

Figure 6. J. C.: Aspergillus — 10.5 hours

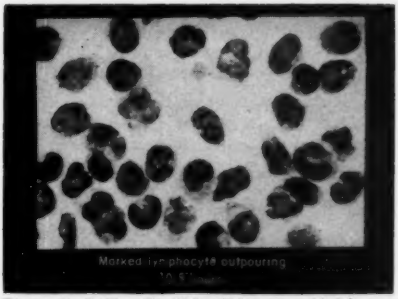

Figure 7. J. C.: Candida albicans — 10.5 hours

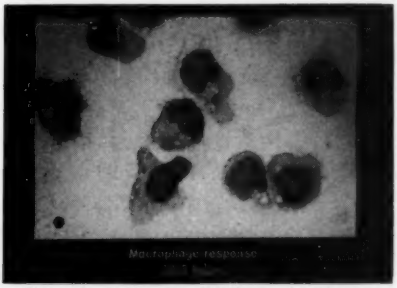

Figure 8. J. C.: Coccidiodin — 10.5 hours

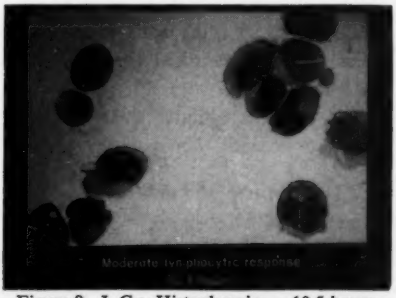

Figure 9. J. C.: Histoplasmin — 10.5 hours

Skin Windows

INTRADERMAL HYPERSENSITIVITY
(Commercially Available Antigens)

20 YEARS AGO AT ONSET	PRESENT REACTION
Candida Albicans—Immediate reaction purpuric center with pseudopodia. (Pathogen) Delayed reaction 24-48 hours. Negative.	Candida Albicans—Immediate reaction purpuric center with pseudopodia. (Pathogen) Delayed reaction 24-48 hours extensive erythema with squamous exfoliation.
Aspergillus—Immediate reaction purpuric center with pseudopodia. (Pathogen) Delayed reaction 24-48 hours. Negative.	Aspergillus—Immediate reaction purpuric center with pseudopodia. (Pathogen) Delayed reaction 24-48 hours extensive erythema with squamous exfoliation.
Coccidioidin—No reaction. (not found on culture) (Cross-reaction to various other fungi).	Coccidioidin—No reaction. (not found on culture)
Histoplasmin—Immediate reaction negative. (not found on culture) Delayed reaction 24-48 hours. 3 cm with no squamous exfoliation.	Histoplasmin—Immediate reaction negative. (not found on culture) Delayed reaction 2 cm. No squamous exfoliation.

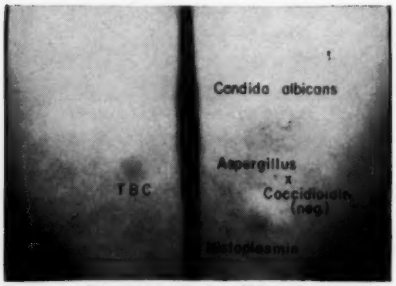

Figure 10. P. C.: Skin test

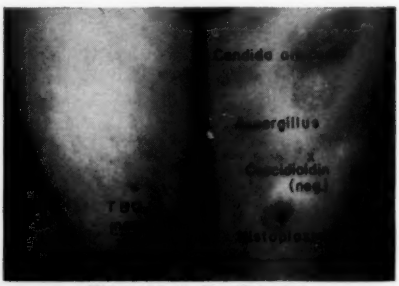

Figure 11. J. C.: Skin test

CLINICAL INTERPRETATIONS

Histoplasma capsulatum was never cultured from any sputa or aspirated bronchial secretions. Intradermal positive hypersensitivity to Histoplasmin (delayed type reaction) was present early in the disease and is still present to a less degree after 20 years.

Candida albicans and Aspergillus niger were cultured repeatedly from bronchial aspirations. The marked immediate intradermal reactions to antigens of these fungi has changed over the 20 years to show extreme hypersensitivity in an extensive erythematous, exfoliative delayed reaction to these fungus antigens showing that they are unquestionably the pathogens for this disease.

The positive Histoplasmin reaction is significant only of its ubiquitous profusion in nature.[5]

Serologic results are unreliable with any presently available commercial fungus antigens except Histoplasmin, because of anticomplement materials which they contain. Complement fixation titres increase after intradermal reaction to the antigens and

therefore true results can be obtained only before intradermal tests are applied. (Fig. 12,13)

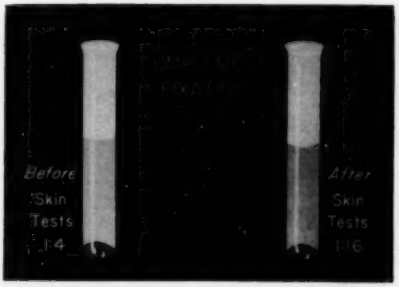

Figure 12. P. C.: Complement fixation titre

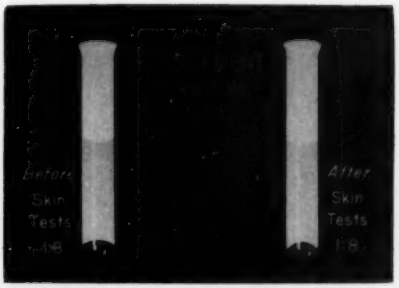

Figure 13. J. C.: Complement fixation titre

The tuberculin (Mantoux) reaction with O.T. and P.P.D. has remained negative in one patient throughout the 20 years of observation. That of the other patient whose disease became more advanced before intensive treatment was initiated has converted in recent years without evidence of a demonstrable tuberculosis lesion. Her contacts with tuberculosis patients have been more intimate because of the need of hospital orthopedic care for management of her transverse myelitis.

Adequate iodide therapy, Sat. Sol. K.I. 5cc. to 20cc. daily, 10% Sol. Sod. iodide I.V., 100cc. daily, Ethyl iodide by inhalation 4cc. q. 2-3 days is the proven treatment of choice for a broncho-pulmonary mycosis of this severity. Antibiotic preparations have not proven effective in conditions of this extent.

Cytology of the exudate after application of antigens by the skin window technique and its proper interpretation according to the cellular type response may serve to indicate the significance of pathogen-antigens in the absence of suitable material for dependable serologic testing. 3,4

REONTGENOGRAPHIC INTERPRETATION

Roetgenograms show "soft" parenchyneal densities from the apices to the bases of the lungs in the acute phase of the disease with progressive changes in healing by condensation into sharply defined nodules. There is progressive calcification of the nodules with a continued stable appearance to the present. The delay in starting controlled intensive treatment for sibling P.C. seems to have permitted progress of the lesions for 2 years. (Figures 14-29)

DISCUSSION

It is believed that the patients were hypersensitive to histoplasmin at the time they became ill because of the prevalence of such hypersensitivity in the general area where they were raised.* Their initial illness is thought to have been "La Grippe" which was epidemic in the community at the time. This illness altered the condition

*Whitehouse et al[5] report a skin testing program conducted among school children in the general area where the patients reported here were raised. Chest films were negative in 75% of histoplasmin positive and tuberculin negative school children. There were 9073 children tested and 90% of them had acquired a positive histoplasmin skin reaction by the age of 14 years. This high incidence helps to clarify the findings of a delayed-type hypersensitivity to histoplasmin in these patients.

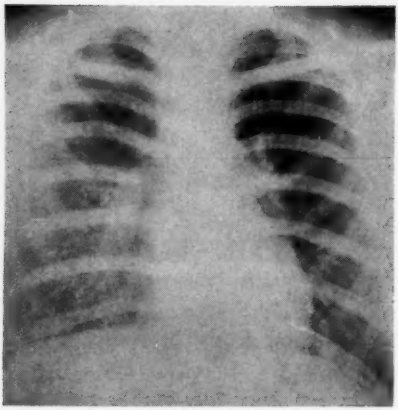

Figure 14. P. C.: 5-28-38. Multiple patches of pneumonitis up to 8 mm. in size are diffusely distributed through the lungs. Lymph nodes are enlarged in the roots and mediastinum.

Figure 15. P. C.: 8-27-38. No change. (No intensive therapy)

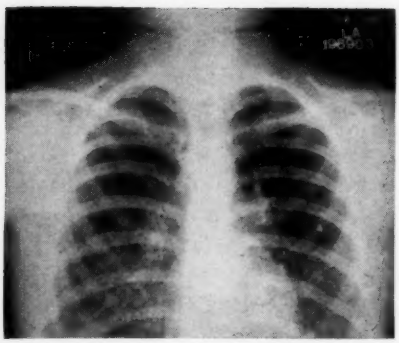

Figure 16. P. C.: 7-16-40. Lesions have increased in size and number; some are more sharply defined. (Intensive therapy has been underway only 2 months.)

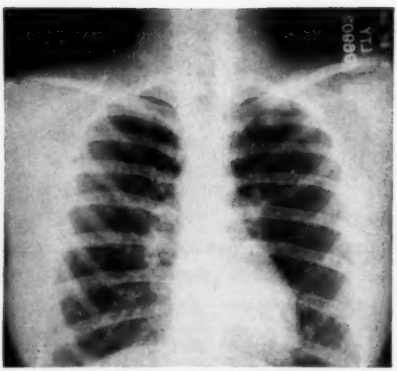

Figure 17. P. C.: 2-25-42. All lesions have decreased in size — upper lobe lesions are starting to calcify.

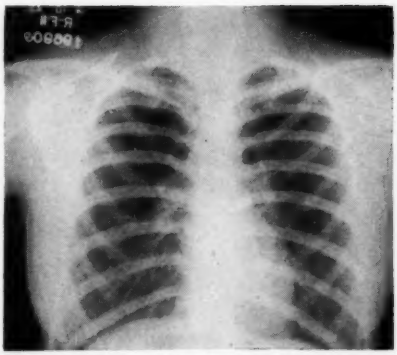

Figure 18. P. C.: 9-10-43. Both parenchymal lesions and nodes have decreased in size. Upper lobe lesions are 50% calcified, but lower lesions are not.

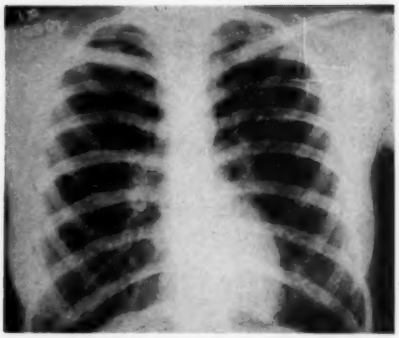

Figure 19. P. C.: 4-26-47. Calcification and resolution progress. Paratracheal nodes are still enlarged.

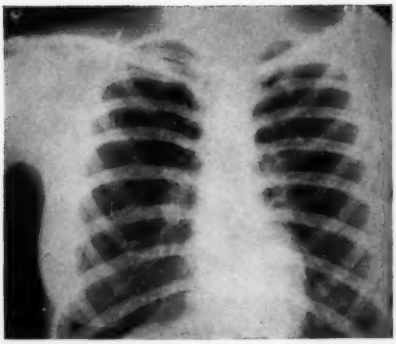

Figure 20. P. C.: 6-23-49. Lower lobe lesions show central calcification.

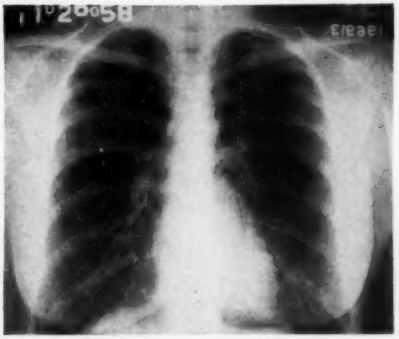

Figure 21. P. C.: 11-26-58. High voltage films: the lesions are all calcified and stable. Minimal node enlargement persists.

Figure 22. J. C.: 4-6-38. Diffuse, uniform distribution of 2-15 mm. patches of density with "soft" borders. Nodes in the mediastinum and ung roots are enlarged.

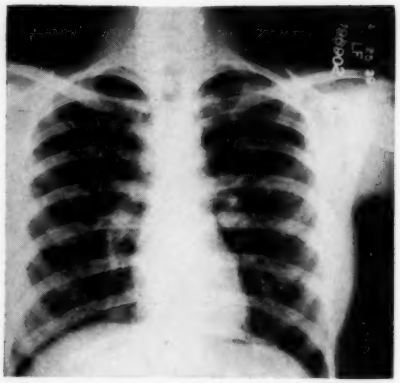

Figure 23. J. C.: 3-25-39. Lymph nodes remain enlarged, but parenchymal lesions have become smaller and more sharply defined.

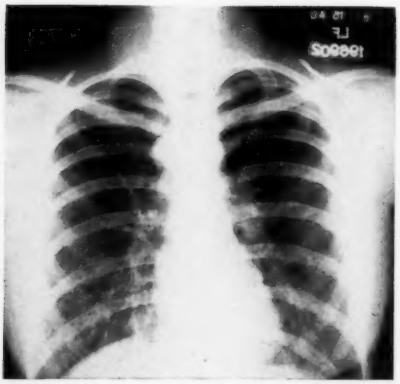

Figure 24. J. C.: 8-15-40. Parenchymal lesions have further decreased in size and are beginning to show central calcification. Lymph nodes are smaller except for one right paratracheal node which has enlarged considerably.

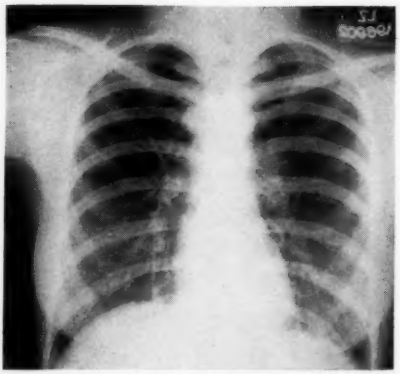

Figure 25. J. C.: 4-30-41. Further decrease in size — more central calcification. Nodes are smaller, but still apparent in the lung roots. Large paratracheal node is unchanged.

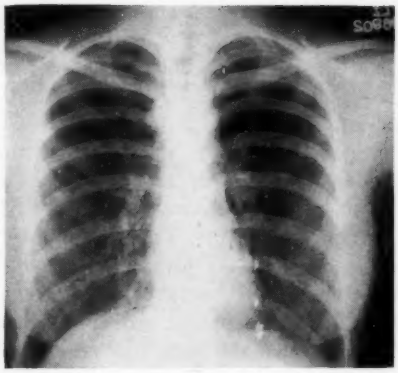

Figure 26. J. C.: 6-6-42. The lesions are at least 50% calcified. The nodes have regressed except the large paratracheal node.

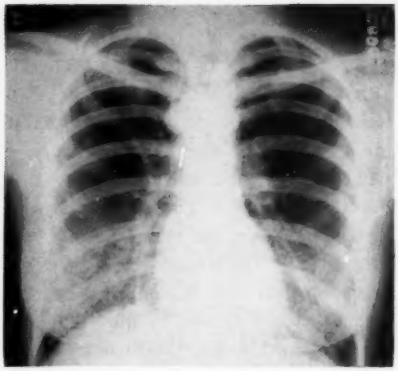

Figure 27. J. C.: 2-26-44. Lesions are almost entirely calcified.

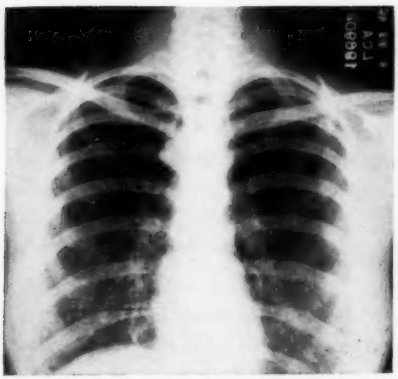

Figure 28. J. C.: 4-23-49. Lesions are completely calcified and stable. Single paracheal node persists.

Figure 29. J. C.: 11-26-58. High voltage technique film: Lesions are unchanged.

of the bronchial mucosa sufficiently to the acid state to permit the feather-born fungi capable of pathogenicity for humans to grow in the lung tissues where they were seeded. This may have been more easily facilitated by their possible histoplasma hypersensitivity. Delayed-type hypersensitivity to the pathogen-antigens developed during the effective treatment with adequate doses of iodides. The progress of its development was a slow process, and some immediate-type reaction is still present although the delayed type reaction to the pathogen-antigens is marked.* This and the lymphocytic cytologic response to the application of these antigens in the skin windows gives support to the opinions expressed by Pappenheimer et al[6] and supported by Good et al[7] that the delayed-type hypersensitivity reaction of tuberculin-type is dependent upon a two-stage process. The response for immediate phagocytosis is demonstrated in the skin window cytologic reaction for the other antigens used in these tests[8,9] The importance of the lymphocytic response to the pathogen-antigens is as hypothesized by Braunsteiner et al[10] if qualified according to work by Eisen et al[11]. Rebuck et al[12] showed by the "skin-window" technique that lymphocsytes may migrate into inflamed areas, hypertrophy and form larger mononuclear cells and even giant cells. Braunsteiner et al[10] confirmed this and found in addition that these derivatives of lymphocytes may then transfer delayed allergy in a highly specific way. Thus a close functional unity beyond morphologic features seems established[14,15]. Five patients who had recovered from ulceroglandular tularemia and who showed marked skin sensitivity of delayed-type to Tularin had "skin-windows" applied. After 30-40 hours the coverslips showed an almost exclusive mononuclear round-cell, epithelioid cell and occasional giant cell in the accumulated exudate. This was scraped and washed off the coverslips with saline and 10-20 million cells from pooled subjects were injected subcutaneously into tularin-negative recipients. The recipients after this injection showed delayed-type hypersensitivity to tularin. The hypothesis derived from these results is stated as follows:

"Certain substances penetrate the organism, specific antagonistic substances are formed in the lymphatic system and fixed on circulating lymphocytes. The chemical nature of these substances is not as yet clear, but there is a fundamental difference from circulating antibodies. Circulating lymphocytes then reach inflammed areas and become mononuclear, epithelioid or even giant cells and help to build up a granulation tissue which contains extremely high amounts of specific antagonistic substances. Thus infection may be localized. Lymphocytic granulomatous reactions of this type seem to play a major role in a variety of chronic infectious diseases, such as tuberculosis, brucellosis, tularemia and others, but intervene probably in all bacterial, fungal and also viral infections.

"Cellular defense mechanisms may, therefore, include three independent, but coordinated systems: immediate non-specific phagocytosis by granulocytes and later by monocytes, cell-bound antagonistic substances carried by lymphocytes and derivated cells, and circulating antibodies elaborated by plasma cells."

*Martin[13] explains the occurence of a negative delayed-type skin response in a patient with severe Candidiasis and also a negative complement fixation test although an immediate-type wheal reaction occurred from the intracutaneous injection of hyperimmune anti-C. albicans serum. He suggests the interpretation that the inhibition of hypersensitivity may be due to an excess of soluable antigen in the tissues.

This hypothesis is further clarified if one enlightens it with the results of work by Eisen et al[11], Pappenheimer et al[6] and Good et al[7] and other observations previously referred to in this paper.

Rebuck and LoGrippo[14] found that subjects inocculated with inactivated poliomyelitis virus antigens (Types I, II and III) responded to the "window" application with an exudate heavily laden with lymphocytes. Non-vaccinated subjects with a low neutralizing antibody titer produced an exudate which contained very few lymphocytes. The lymphocyte response could be correllated with the neutralizing antibody titer in those tested. In unvaccinated persons the exudative response to 0.02 ml of poliomyelitis virus-inactivated vaccine (prototype III) was dominated by neutrophiles for the first 12 hours and then macrophages became the dominant cell type. At no time up to 24 hours were there more than a few lymphocytes. In contrast a polio III vaccinated individual with 1:256 neutralizing antibody titer, showed a large number of lymphocytes about 9 hours after "window" application of the vaccine. The lymphocytes began to hypertrophy at 12 hours but continued to dominate the cytological picture until the 24th hour.

Eisen et al[11] attempted to clarify some of the confusion that exists in the explanation of the significance of a delayed-type hypersensitivity response. He explains that this reaction does not seem to be dependent upon serum antibody but upon antibody substances associated with cells. Pappenheimer and associates[6] assume that antigen is retained by cells to "alter specifically gamma globulin synthesis."

Iodides meet the criteria which have been emphasized as requirements for fungicidal or fungistatic agents[17,18]. They must so alter through changes in metabolic and physiologic requirements for growth and reproduction of the cellular components of the fungus that it becomes non-pathogenic; but in doing so must not be toxic or cause damage to the tissue cells of the host. These requirements seem to have been met in these patients. The disease has been arrested and they show no evidence of toxic ill effects from the treatment.

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CARCINOMA OF THE PANCREAS WITH UNUSUAL CENTRAL NERVOUS SYSTEM COMPLICATIONS. CLINICAL PATHOLOGICAL CONFERENCE

ROBERT K. NIXON, M.D.* BOY FRAME, M.D.* AND JOSE BEBIN, M.D.**

CASE PRESENTATION — (Dr. Nixon)

A 61 year old white male parking lot employee was seen in the Henry Ford Hospital Emergency Room complaining of "blind staggers". He gave a history of having pain in the sacral region during the preceding 3 months. The pain did not radiate. Three weeks before admission the patient had a head cold with a cough which aggravated the numbness of the anterior aspects of both legs down to the knees. One week before admission the patient began to experience a spinning sensation while standing on a ladder painting with his head in a hyperextended position and this the patient referred to as "blind staggers". He had continued to notice this sensation and it was usually associated with looking upward. Approximately 2 days after the onset of the dizziness, the patient noted a frontal headache and this gradually increased. At the time of admission, the patient stated that he felt "sea sick and nauseated". There had been no vomiting. He had taken a considerable number of aspirins without relief. There had been no tinnitus or hearing loss, no aphasia, dysarthria, bowel or bladder disturbance, or seizures and no weight loss.

Past history: In 1939 patient was in V. A. Hospital for 3 months with a diagnosis of "nervous neuritis". In 1921 a T & A was done and afterwards he spent 3 months in the V. A. Hospital because of albuminuria. There was no history of high blood pressure. The patient was known to have a mediastinal mass for the past 19 years which had been checked frequently at Herman Kiefer Hospital and was thought to be of no importance.

Physical Examination: Blood pressure 140/92, pulse 20 to the quarter and regular, temperature normal, thyroid not enlarged, lungs clear to P & A, heart not enlarged, N.S.R., no murmurs heard. Abdominal examination negative, rectal examination showed prostate enlargement of 1 plus.

Neuorlogical examination: Gait normal. Patient able to do heel and toe walking well and tandem walking fairly well. On Romberg the patient had a sway but did not fall. Funduscopic revealed normal disc with grade 1 angiopathy. No hemorrhages or exudates were present. The first cranial nerves were intact. A definite positional nystagmus in the lateral plane which changed direction on turning the patient's head to the opposite side was noted. A minimal vertigo element was present with the nystagmus on one occasion. Visual fields were grossly intact. The pupils round, regular and equal and react to L & A. There was a questionable diminution of the right corneal reflex. 5th, 7th, 8th, 9th, 10th, 11th and 12th cranial nerves were intact. The deep tendon reflexes were all 3 plus active with the exception of a questionable decrease in the left biceps. Hoffman sign was positive bilaterally. Abdominal reflexes, Cremasterics were present. Both plantars were down-going. The

*Division of General Medicine.
**Division of Neurology and Psychiatry.

muscle strength was good in all extremities. There was some adiadochokinesis of the right hand and slight impairment of the heel-shin test on the right was present. No bruits were heard. There was some definite percussion tenderness over the left frontal area. Position, light touch, pain and vibratory sense were intact. No evidence of atrophy or fasciculations was seen.

The patient was admitted and the following studies were obtained: Hemoglobin 15.4 gms., WBC 8,600 with normal differential, urinalysis negative, BSP 4%, liver flocs. negative, bilirubin total .32 mgms. Sed. rate 10, cold agglutinins negative. Psittacosis complement fixation titer negative, febrile agglutinins negative. VDRL negative. 3 L.E. preps. negative. Three stools for occult blood negative. Pletelet count normal. Skin tests for monilia, mumps, and histoplasmin positive. Mumps complement fixation test neg. Two lumbar punctures were done. The first contained 23 WBC with 18 polys and 5 monos, protein 106, sugar 75 with a simultaneous blood sugar of 180. Second L.P. showed: protein 37, cell count 84 with 77 monos and 7 polys.

Culture of cerebrospinal fluid negative. No acid fast bacilli seen on smear. Cytology of the cerebrospinal fluid negative, for malignant cells. Special smear: platelets adequate, 1 band, 72 neutrophils, 1 eosinophile, 16 lymphocytes, 10 monocytes, essentially normocytic. No hematuria. PPD positive. Serum proteins 6.6 with 3.84 albumin and normal globulin fractions. Two repeat urinalyses negative.

Chest x-ray: large calcified node in subcranial area. Fairly well circumscribed infiltrate in the left upper lobe which was present on film taken 1 year previously and non-increased in size. Skull film essentially negative. Sinus films: soft tissue mass in the nasopharynx. Lumbar spine films; mild rotoscoliosis involving the lumbar spine. Defect involving the pars media of the 5th lumbar vertebrae seen on the right. Laminograms of the left hilum showed slight elevation of the left bronchus. Repeat chest x-ray 1 month later showed no change.

Pneumoencephalogram: mild cortical atrophy. EEG: negative. Biopsy of nasopharyngeal mass revealed chronic inflammation of nasal mucosa. Repeat biopsy — same report. Muscle biopsy from left leg showed fibrofatty tissue and muscle. Bronchoscopy: negative. Bronchial washings negative on Pap. smear and negative culture for AFB. Gastric washings negative for AFB on culture. Sputum negative on smear and culture, for AFB. Fungus cultures of sputum negative. Bacterial culture of sputum showed normal flora.

Course in the hospital: The patient was anorexic and seemed to stagger when he walked. He complained of persistent headaches and general malaise. He was noted to lie in bed with his legs drawn up on the abdomen as if this was the position of maximum comfort and complained of backache. Toward the end of the hospital stay some fasciculations were noted in the left calf.

Following discharge the patient became worse and was admitted to a V. A. hospital four weeks later. There he complained of an increasingly severe pain in the back and hip and difficulty in swallowing. He was noted to have slurred speech and shuffling gait and was ataxic. The left pupil was larger than the right and did

not react to light and accomodation. There was slight ptosis of the left lid. The uvula and soft palate deviated to the right on phonation. The tongue also deviated to the right. Liver palpable 1 finger breadth below right costal margin. Poor rectal spincter tone. Bilateral inguinal nodes and soft nodes in the left axilla were noted. A positive Romberg was present. Reflexes were present and bilaterally equal. A slight adiadochokinesia was present bilaterally. No anesthesia noted. X-rays at the V. A. revealed streaky densities resembling fibrotic deposits in the left upper lobe. X-ray of the lumbar spine revealed a fracture of the upper plate of the body of L3 on the right. Laminograms of the left upper lobe revealed an irregular cavitating mass.

At the V. A. hospital, the patient noted increasing difficulty in starting his urinary stream and passing feces. He developed inability to swallow and intubation was necessary. He expired quitely following what appeared to be a bout of aspiration pneumonitis.

DISCUSSION — (Dr. Frame)

For today's Clinical Pathologic Conference, we have a 61 year old male with apparent pathology in the mediastinum, the lungs, central nervous system and bones. In addition, there was a mass in the nasopharynx, which was negative for malignancy on two biopsies. Our problem is to define the pathology in each of these areas and, if possible, try to connect them into one etiology.

A large, calcified mass had been present in the superior mediastinum for at least 19 years. There were no characteristic calcifications of a teratoma. The features of the mass with the diffuse calcification suggest the possibility of a large calcified node, due to chronic infection, with tuberculosis and histoplasmosis, as the best possibilities. This mediastinal mass may or may not be related to the pulmonary pathology.

Let us next evaluate the infiltrate in the left upper lung field. We are told very little in the way of respiratory symptoms or physical findings, so we will have to concentrate primarily on the x-rays. This infiltration had been present for at least one year and seemed to increase slightly in size and, terminally, cavitation was suggested. The main differential seems to be whether this infiltration was chronic infection or malignancy. The slowly progressive course over a period of a year is perhaps more compatible with chronic infection, such as tuberculosis or histoplasmosis, which may have broken down terminally into cavitation. However, the many negative sputum and culture studies for acid fast and fungi would be somewhat unusual in a progressive active infection of this nature. Secondary to the patient's neurologic disease was moderate dysphagia. This brings up the possiblity of aspiration pneumonitis, which occasionally does occur in the upper lobes, particularly in a patient who is confined to bed. The pneumonitis may have broken down and resulted in a pyogenic abscess; or possibly a foreign body with pulmonary abscess could have been present.

The other strong possibility in this patient, to explain the infiltrate in the left upper lobe, is that of pulmonary neoplasm. The negative bronchoscopy and smear for tumor cells is somewhat against this diagnosis but does not rule it out. The absence

of any pulmonary symptoms whatever is somewhat unusual in pulmonary neoplasm. The other consideration would be the presence of a chronic infection, such as tuberculosis plus superimposed pulmonary neoplasm, either primary or metastatic. Such a combination is being described more frequently in the literature. We can only conclude at this point that the available information does not readily separate the diagnosis of tumor from chronic apical tuberculosis and that the presence of both is a good possibility.

At this point, let us consider the pathology of the central nervous system. We have essentially a spotty cranial nerve involvement with signs of cerebellar insufficiency, associated with pleocytosis and a variable elevation of the cerebrospinal fluid protein. There were no signs of meningeal irritation but, nevertheless, the presence of chronic meningitis has to be strongly considered. An infectious agent, such as tuberculosis or torula, could possibly give a basilar meningitis with spotty cranial nerve involvement and the pleocytosis of the spinal fluid. However, the absence of a specific agent on direct smear and culture is strong evidence against the presence of such an infectious meningitis. In addition, the absence of a more striking reduction of the cerebrospinal fluid sugar is additional evidence against such a diagnosis.

Another consideration to explain at least part of the central nervous system involvement would be that of a meningeal carcinomatosis from possibly carcinoma of the lung. The cranial nerve involvement, in addition to the cerebrospinal fluid changes are compatible with this, but ordinarily in this condition, the cerebrospinal fluid sugar is also frequently lower than that reported here. However, to be taken into consideration is the fact that the blood sugar, at the same time the cerebrospinal fluid sugar was determined, was moderately elevated. The patient had quite striking evidence of cerebellar insufficiency. This raises the possibility of metastatic disease to the cerebellum but there were no headaches or signs of increased intracranial pressure. We, therefore, consider strongly the possibility of a cerebellar degeneration, which is being described more and more frequently with various malignancies. This is a strange type of degeneration that may occur in the cerebellum, the long tracts of the spinal cord, the peripheral nerves and muscle in a variety of malignancies without actual metastatic invasion of these organs. The pathogenesis of this condition has not as yet been defined.

We must consider other sources for metastatic spread to the central nervous system. We are told of a nasopharyngeal mass. This must have been quite impressive since the nose and throat consultant biopsied this mass on two occasions. The mass also looked quite impressive on the skull x-ray. We ask ourselves if this patient could have a primary carcinoma in the nasopharynx, the so called Schmincke's tumor, which spread to the central nervous system. The spotty type of cranial nerve involvement and the pleocytosis in the spinal fluid is classic for this type of tumor. The negative biopsy does not disturb us, since it is well known that these tumors may be quite difficult to biopsy and several negative biopsies are not unusual. The lack of local signs relating to obstruction of the nares or internal auditory meatus also should not deter us from making this diagnosis, since tumors are frequently silent and may give no local clue as to their presence. Distal metastases to bone

are common in this type of malignancy and this might well be the explanation of the persistent progressive back and hip pain. The negative skull x-rays are somewhat disconcerting but, again, this tumor may invade the various foramina at the base of the skull impairing the function of one or more cranial nerves without causing any actual erosion of the skull. Ordinarily, these tumors spread locally to the cervical lymph nodes; none were described in this patient. However, about a third of these patients in some series have no cervical lymph node involvement. So on the basis of the information, we would have to strongly consider the possibility of a nasopharyngeal carcinoma with spread to the central nervous system, bone and possibly lung.

Another possibility is that a primary pulmonary neoplasm, which has already been discussed, could metastasize to the nasopharyngeal area and then spread to the central nervous system, as outlined for primary nasopharyngeal tumor.

In addition to the above considerations, we would like to list several possibilities which one might consider as he reads the protocol but for which information is not sufficient to make a definite diagnosis:

1. A malignant degeneration of a teratoma with spread to the left upper lung and central nervous system, but again, the calcification in the mediastinal mass is not that of a teratoma.

2. We considered the possibility of a granulomatous process in the nasopharynx and lung, something in the nature of a necrotizing vasculitis or Wegener's arteritis but, ordinarily this gives an ulcerative process in the nasopharynx in association with peripheral neuritis and a terminal glomerulitis.

3. One must consider unusual fungus infections involving the nasopharynx, the lung and the central nervous system. We are told of one elevated blood sugar but are given no other information with regards to the possibility of diabetes-mellitus. Nevertheless, one particular type of fungus, namely mucormycosis, has a predilection for the nasopharynx, as well as lung and seems to occur more frequently in the presence of diabetes.

4. Terminally, inguinal and axillary nodes were described, which raises the possibility of a lymphoma which could spread to the central nervous system in such a fashion depicted.

5. We are told that the patient preferred to lie with his legs drawn up over the abdomen, as the position of maximum comfort. This unusual position raises the possibility of a retroperitoneal neoplasm, especially in the pancreas, which might then spread to bone, lung and central nervous system, as already described. However, with no further information given, we can only offer this as speculation.

We must then, of the various possibilities suggested, try to make a final diagnosis in this case. It is difficult to be dogmatic, but two possibilities seem to be foremost: *One*, that the patient had a primary pulmonary neoplasm with metastatic spread to the meninges of the central nervous system, bone and possibly the nasopharynx; the tumor then spread from the nasopharynx to the base of the brain giving rise to the

cranial nerve involvement. The *second* possibility would be a primary nasopharyngeal carcinoma which spread to the lungs, bones and central nervous system; statistically, the former would be the more common. We believe that, in addition, the cerebellar symptomatology in this patient is on a degenerative basis, secondary to malignancy without actual metastatic invasion of the cerebellum. Since the pulmonary picture, particularly the radiologic findings, seem somewhat more compatible with an infectious process, we wonder if the patient did not have additional infection in the upper lobe, either reactivation of tuberculosis or terminal aspiration pneumonia and abscess.

DISCUSSION AFTER PATHOLOGY

This case demonstrates how silent carcinoma of the pancreas can be. Ordinarily, with this neoplasm one expects greater weight loss and abdominal pain, but obviously, it can occasionally behave in a fashion as described by Dr. Bebin. Unfortunately, the nature of the nasopharyngeal mass, indeed if there even was one, must remain an enigma since this area was not examined at autopsy.

FINAL PATHOLOGICAL DIAGNOSES — (Dr. Bebin)

Aspiration pneumonia and multiple lung abscesses (cause of death); Left pleural effusion; Adenocarcinoma of the head of the pancreas with carcinomatosis: Meningeal, Cerebrospinal, Lung, Adrenal, Bone (lumbar spine); Generalized arteriosclerosis; Multiple retention cysts of the left kidney.

The autopsy was performed at the Veterans' Administration Hospital in Dearborn, Michigan. There were no unusual findings on the external examination of the body. The left pleural cavity contained 200 cc. of clear, bloody fluid and a few fibrous adhesions in the apical regions. The protocol does not mention the mediastinal mass found in the x-ray examination. The lungs were described as being heavy and firm. They did not collapse on opening of the chest. The pleural surface of both lungs were thick and opaque. On section of the lungs, the cut surfaces were marred with many red-yellowish areas of increased density. Multiple abscesses were also present throughout the lung fields; these were filled with a semi-solid yellowish pus; however, the exudate was odorless. Only the upper lobe of the right lung contained a substantial amount of air. On microscopic examination, almost the entire lung parenchyma was replaced by a diffuse aspiration type of pneumonitis and multiple abscess. In some areas between the inflamatory processes there were foci of metastic neoplasm with the characteristics of an adenocarcinoma very similar to the one found in the pancreas.

The heart and vascular system were considered normal except for a moderate degree of arteriosclerosis. The gastrointestinal system, the liver and the spleen were normal on microscopic examination. The pancreas was normal in size and shape. The head of the pancreas appeared to be much more firm than the remaining portions of this organ. The parenchyma of this portion has lost its normal architecture, contrasting with the normal appearance of the body and the tail of this organ. On microscopic examination, the parenchyma of the head of the pancreas was replaced by a neoplasm made up of duct-like structures lined by columnar and sometimes cuboidal cells, supported by a dense, fibrous stroma. In some of the nerves of the

peri-pancreatic tissues there was marked invasion by neoplasn. This tumor was classified as a ductal adenocarcinoma arising from the head of the pancreas.

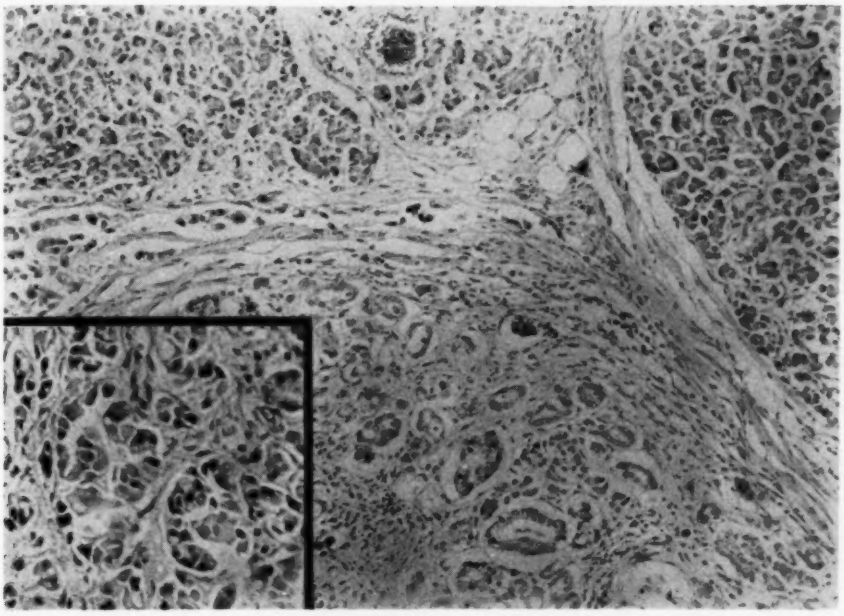

Figure 1
Ductal Adenocarcinoma of head of pancreas.

The genital-urinary system was unremarkable except for a few small retention cysts filled with clear greenish fluid present in the left kidney. The endocrine system was normal except for the right adrenal gland which, on microscopic examination, showed evidence of metastatic invasion by the pancreatic neoplasm. The vertebral body of the lumbar spine revealed a replacement of the bone marrow by tumor.

Central nervous system; the brain weighed 1300 grams and was described as moderately atrophic and congested throughout. On the left occipital lobe there was a 5 mm. metastatic lesion. No other focal lesions were seen on the cerebrum, brain stem, or cerebellum. The circle of Willis showed moderate arteriosclerosis. The leptomeninges of the brain and, particularly of the spinal cord, demonstrated diffuse infiltration by neoplastic elements mingled with some inflammatory cells. The neoplastic cells were several layers thick around the anterior spinal artery and the spinal menings. They also infiltrated heavily the spinal roots and the spinal ganglia. Similar neoplastic elements were found infiltrating the meninges at the base of the brain and especially around the brain stem and the cranial nerves.

There was some congestion throughout the brain. In the left occipital lobe around the metastasis there was considerable edema. The tumor itself was very similar to the pancreatic tumor. The cerebellar cortex showed areas with loss of

granular and purkinje cells, and occasional nests of neoplastic cells. There was some degeneration of the marginal zone of the spinal cord, particularly in the areas adjacent to the more heavily infiltrated meninges.

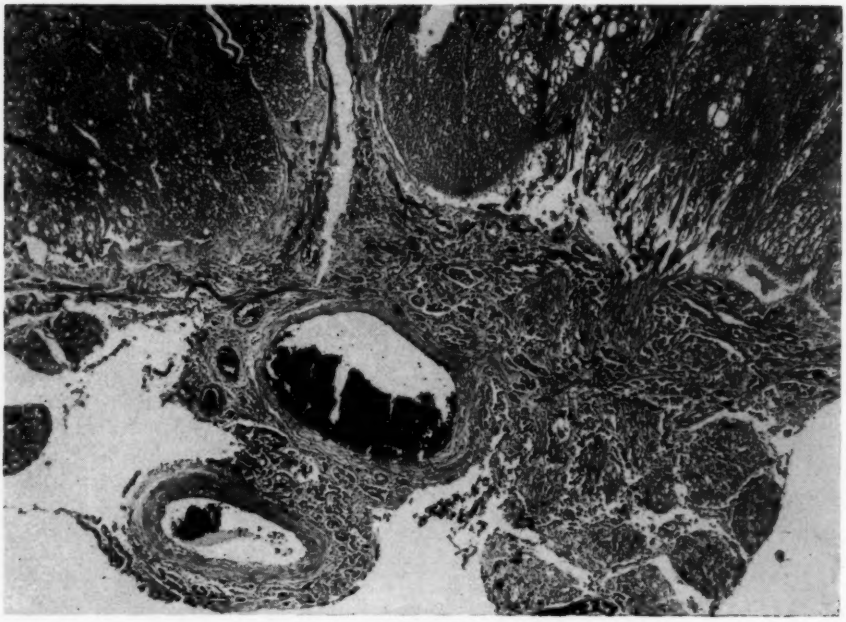

Figure 2

Ventral surface of spinal cord. Invasion of leptomeninges and spinal roots by carcinoma.

This case illustrates very well the difficulties in diagnoses of some of the pancreatic tumors particularly when they are not accompanied by jaundice as one of its clinical manifestations. The silent nature of the primary tumor and the frequency of symptoms referable to metastases have been already especially emphasized by Duff.[1] The ductal adenocarcinomas of the pancreas are the most common neoplasm of this organ. They constitute 81 per cent, according to Miller and Baggenstoss,[2] of all primary carcinomas of the pancreas and they arise more frequently in the head (71 per cent). Jaundice was found to occur in 128 out of 144 cases of carcinoma of the pancreas (89 per cent). The invasion of the perineural lymph-spaces occurs in 73 per cent of all cases.

The neurological manifestations with carcinoma of the pancreas as well as with other visceral cancers are due, in general, to invasion of the nervous system and its meninges. In recent years the association of neurological symptoms with carcinoma without invasion of the nervous system has been emphasized. Three types of pathological changes seem to occur more frequently:

1. Subacute degeneration of the cerebellar cortex described by Greenfield[3] in 1934 with degeneration and disappearance of purkinje cells and loss of granular cells;

2. Peripheral neuropathy and myelopathy, occurring mainly as sensory neuropathy and described by Denny-Brown[4] in 1948;

3. Myasthenia-like symptoms described by Denny-Brown[4] and by Henson[5] with nonspecific changes in the muscle and with no tumor of the thymus.

The case presented today has combined features of both direct spread of a carcinoma to the other organs as well as the central nervous system and also of the features of a subacute degeneration of the cerebellar cortex.

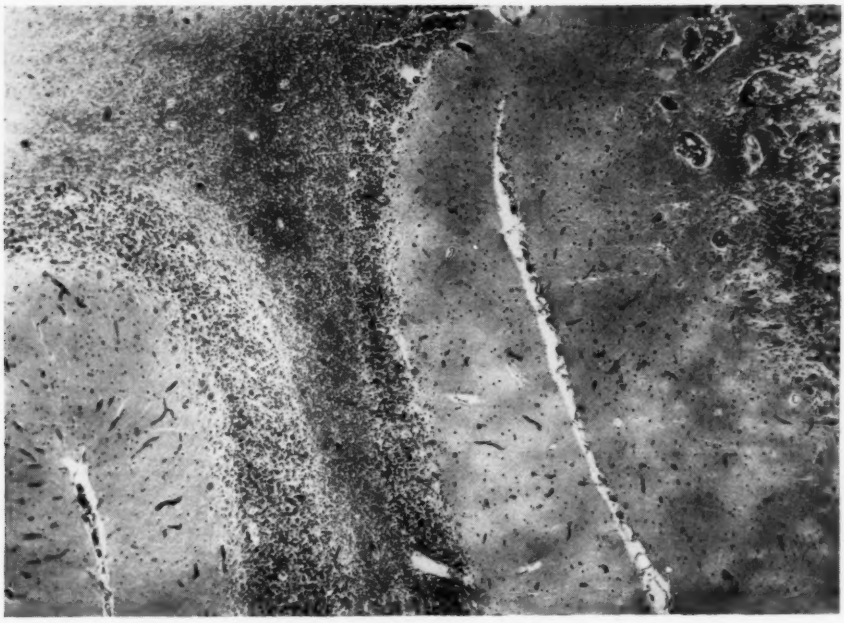

Figure 3

Cerebellar cortex. Loss of Purkinje and granular cells. Nests of neoplastic cells.

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2. Miller, J. R., Baggenstoss, A. H., and Comfort, M. W.: Carcinoma of the pancreas. Effect of histological type and grade of malignancy on its behavior, Cancer 4:233, 1951.

3. Greenfield, J. G.: Subacute spino-cerebellar degeneration occurring in elderly patients, Brain 57:161, 1934.

4. Denny-Brown, D.: Primary sensory neuropathy with muscular changes associated with carcinoma, J. Neurol., Neurosurg. & Psychiat. 11:73, 1948.

5. Henson, R. A., Russell, D. S., and Wilkinson, M.: Carcinomatosis neuropathy and myopathy; a clinical pathological study, Brain, 77:82, 1954.

SCIENTIFIC AWARDS

Dr. O. H. Gaebler, Head of the Biochemistry Department, Edsel B. Ford Institute for Medical Research, received the Ernest Bischoff Award in Clinical Chemistry at the meeting of the American Association of Clinical Chemists in Cleveland, August 27-29. His acceptance address was entitled, "Adventures in Clinical Chemistry." This Award is given annually to a chemist on the staff of a hospital or clinical laboratory who has distinguished himself by achievement and devotion and has helped solve those chemical problems which arise daily in the practice of the medical arts.

At the Annual Meeting of the American Gastroenterological Association in Atlantic City on June 6, 1959 Dr. Robert J. Priest was awarded the B. B. Vincent Lyon Prize for the best piece of research presented by any Associate Member of this Association. The research was entitled, "A New Qualitative Defect of Leukocyte Function in Ulcerative Colitis." Co-authors with Dr. Priest were Dr. John W. Rebuck, Department of Laboratories and Gerald T. Havey, Department of Medicine.

THE AMERICAN COLLEGE OF PHYSICIANS

4200 Pine Street, Philadelphia 4, Pennsylvania

PRESENTS

POSTGRADUATE COURSE No. 6

INTERNAL MEDICINE — SELECTED SUBJECTS

January 25-29, 1960

Henry Ford Hospital
Detroit, Michigan

MEETING PLACE
The Main Auditorium
Clinic Building

Director
JOHN G. MATEER, M.D., F.A.C.P.

Associate Director
CLARENCE E. RUPE, M.D., (Associate)

(Minimal Registration, 40;
Maximal Registration, 120)

Fees A.C.P. Members, $60.00; Non-members, $80.00

COURSE No. 6
INTERNAL MEDICINE — SELECTED SUBJECTS
OFFICERS OF INSTRUCTION

(All participants are members of the Staff of the Henry Ford Hospital unless otherwise indicated.)

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HERNAN ALVAREZ, M.D., Division of Cardiology.
J. EDWARD BERK, M.D., F.A.C.P., Director, Department of Internal Medicine, Sinai Hospital of Detroit, Detroit, Mich.
ROBERT E. BIRK, M.D., Fourth Medical Clinic.
MELVIN A. BLOCK, M.D., F.A.C.S., Division of General Surgery.
GERALD M. BRENEMAN, M.D., Division of Cardiology.
MICHAEL J. BRENNAN, M.D., (Associate), Division of Oncology.
GEOFFREY E. BRINKMAN, M.D., Pulmonary Division.
JOHN B. BRYAN, M.D., (Associate), Metabolic Division.
ROBIN C. BUERKI, M.D., F.A.C.P., Executive Director.
JOHN R. CALDWELL, M.D., Division of Hypertension.
E. OSBORNE COATES, JR., M.D., F.A.C.P., Pulmonary Division.
JAMES M. COLVILLE, M.D., (Associate), Division of Infectious Diseases.
J. DANA DARNLEY, M.D., Division of Neurology.
LAURIE C. DICKSON, M.D., (Associate), Third Medical Clinic.
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ROBERT H. DURHAM, M.D., F.A.C.P., Division of General Medicine.
DWIGHT C. ENSIGN, M.D., F.A.C.P., Division of Arthritis.
WILLIAM R. EYLER, M.D., Department of Radiology.
LAURENCE S. FALLIS, M.D., F.A.C.S., Department of Surgery.
BOY FRAME, M.D., (Associate), Division of General Medicine.
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CLARENCE S. LIVINGOOD, M.D., Department of Dermatology.
JOHN G. MATEER, M.D., F.A.C.P., Department of Medicine.
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JOHN W. REBUCK, M.D., Department of Laboratories.
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JOHN W. SIGLER, M.D., F.A.C.P., (Associate), Division of Arthritis.
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FRED W. WHITEHOUSE, M.D., (Associate), Metabolic Division.
GEORGE M. WILSON, M.D., (Associate), Division of Arthritis.
THEODORE E. WOODWARD, M.D., F.A.C.P., Professor of Medicine, University of Maryland School of Medicine, Baltimore, Md.
ROBERT F. ZIEGLER, M.D., Division of Pediatric Cardiology.

This course has been constructed to present to the internist selected current developments in the field of internal medicine. The biochemical, pathophysiological and surgical aspects of diseases will be discussed when indicated. Emphasis has been placed upon diseases of the cardiovascular system, the endocrine glands, the gastrointestinal tract, infections, hematology, pulmonary diseases, the collagen diseases, conditions involving the joints and other subspecialty fields.

The various conditions will be discussed by those having special knowledge and experience in the subject under discussion. Numerous panel discussions have been arranged and, wherever possible, an effort has been made to schedule more or less related subjects in sequence.

In addition to the numerous discussions to be presented by members of the teaching staff of the Henry Ford Hospital, there will be certain presentations by eminent guest speakers. Opportunity for questions and answers will be provided after each paper.

Anyone wishing to enroll in this course should apply to Mr. Edward R. Loveland, American College of Physicians, 4200 Pine St., Philadelphia, 4, Pa.

OUTLINE OF COURSE

Monday, January 25

A.M. Session

8:00 Registration.

9:00 Remarks of Welcome.
Dr. Buerki.

9:05 Introduction and Announcements.
Dr. Mateer.
Chairman, Morning Session:
Dr. R. Smith.

9:15 Partial Hypophyseal Failure.
Dr. R. Smith.
Discussion.

9:40 Recognition and Management of Latent Adrenal Cortical Insufficiency.
Dr. Jailer.
Discussion.

10:15 Acquired Virilism.
Dr. Mellinger.
Discussion.

10:40 Intermission.

10:50 Stress Polycythemia.
Dr. Nixon.
Discussion.

11:15 Pathophysiology of Subacute Thyroiditis.
Dr. Miller.
Discussion.

11:40 Panel: Selected Aspects of Glucocorticoid Therapy.
Drs. R. Smith, Jailer, Woodward and Ensign.

12:30 Luncheon.

1:30 Tour of Clinic and Laboratories.

P.M. Session
Chairman: Dr. Quinn.

2:30 General Principles in the Diagnosis and Management of Infectious Diseases.
Dr. Woodward.
Discussion.

3:05 The Antistaphylococcal Agents.
Dr. Colville.
Discussion.

3:30 Experience with Antibiotic Therapy of Subacute Bacterial Endocarditis.
Dr. Quinn.
Discussion .

3:55 Intermission.

4:05 The Treatment of Superficial Fungus Infection of the Skin with Griseofulvin—a New Agent.
Dr. Livingood.
Discussion.

4:30 Practical Chemotherapy for the Internist in Neoplastic Disease.
Dr. Brennan.
Discussion.

Tuesday, January 26

A.M. Session.

8:00 Medical Staff Meeting.
Dr. Mateer.

9:00 Intermission.
Chairman, Morning Sessions
Dr. Keyes

9:10 Pathophysiology of Congestive Failure.
Dr. Hellems.
Discussion.

9:35 Mechanism of Action of Diuretics.
Dr. Keyes.
Discussion.

10:00 Refractory Heart Failure.
Dr. Drake.
Discussion.

10:25 Intermission.

10:35 Clinical Features of Rarer Types of Heart Disease.
Dr. Breneman.
Discussion.

11:00 Diagnosis of Mitral Insufficiency with Special Reference to Murmurs.
Dr. Morgan.
Discussion.

11:25 Panel: Mitral Commissurotomy.
Drs. Keyes, Drake, Lam, Alvarez and Morgan.

12:30 Luncheon.
Informal Discussion:
The Philosophy of Management of Patients with Coronary Artery Disease.
Dr. Dickson.
Problems in Biliary Tract Diagnosis.
Dr. Priest.
Management of Rheumatoid Arthritis.
Dr. Wilson.
Management of Allergies.
Dr. Shaffer.
Hypokalemia.
Dr. P. Smith.

P.M. Session
Chairman: Dr. Drake

2:00 Pitfalls in Interpretation of Cardiac Catheterization Data.
Dr. Ziegler.
Discussion.

2:25 Radiographic Aids in the Diagnosis of Cardiac Abnormalties.
Dr. Eyler.
Discussion.

2:50 Coronary Anatomy for the Practicing Internist.
Dr. James.
Discussion.

3:15 Intermission.

3:30 Seminar:
Selection of Patients for Cardiac Surgery.
Drs. Keyes, Lam, Eyler, Green and Drake.
or: Seminar:
EKG Interpretation.
Drs. Morgan, Ziegler, Alvarez and James.

Wednesday, January 27

A.M. Session

8:00 Surgical Staff Conference.
Dr. Fallis.

9:00 Intermission.
Chairman: Dr. Monto.

9:10 Ultrastructural Diseases of the Blood.
Dr. Rebuck.
Discussion.

9:45 Clinical Disorders of Platelet Malfunction.
Dr. Monto.
Discussion.

10:10 Panel: Management of the Hemorrhagic Diseases.
Drs. Monto, Abraham, Johnson and Rebuck.

10:50 Intermission.

11:05 Clinical and Experimental Experiences with Grafts and Prostheses in Management of Otosclerosis.
Dr. Schuknecht.
Discussion.

11:30 The Role of Glucagon in Clinical Medicine.
Dr. Whitehouse.
Discussion.

11:55 Diagnostic Features of Pancreatic Disease.
Dr. Berk.
Discussion.

12:30 Luncheon.
Informal Discussion:
Therapy of Hypertension—Newer Aspects.
Dr. Caldwell.
Headache and its Management.
Drs. Noshay and Darnley.
Management of Lymphoma and Leukemia.
Dr. Van Slyck.
Sign-posts in Diabetes.
Dr. Bryan.
Medical Disability.
Dr. Steiner.

P.M. Session

SYMPOSIUM ON MALABSORPTION
Chairman: Dr. Mateer.

2:00 Physiology of Absorption and Electron Microscopy of Small Bowel Biopsy.
Dr. Haubrich.
Discussion.

2:25 Classification and Symptomatology of Malabsorption States.
Dr. Pollard.
Discussion.

2:50 Practical Value of Absorption Tests in the Differential Diagnosis.
Dr. Rinaldo.
Discussion.

3:15 Intermission.

3:25 Roentgen Ray Findings.
Dr. Eyler.
Discussion.

3:45 Therapy.
Dr. Priest.
Discussion.

4:10 Panel Discussion of Malabsorption.
Drs. Priest, Haubrich, Pollard and Rinaldo.

Thursday, January 28

A.M. Session
Chairman: Dr. Rupe.

9:00 The Sicca Syndrome.
Dr. Birk.
Discussion.

9:25 Variants of Systemic Lupus Erythematosus.
Dr. Haserick.
Discussion.

10:00 The L-E Phenomenon in Rheumatoid Arthritis.
Dr. Sigler.
Discussion.

10:20 Variants of Rheumatoid Arthritis.
Dr. Robinson.
Discussion.

10:55 Intermission.

11:05 Some Considerations of the Granulomatous Reaction.
Dr. McColl.
Discussion.

11:30 Panel: The Collagen Diseases.
Drs. Rupe, Robinson, Haserick, Livingood and Ensign.

12:30 Luncheon.
Informal Discussion:
Postmenopausal Osteoporosis.
Dr. R. Smith.
Menstrual Irregularity.
Dr. Mellinger.
Skin Manifestations Associated with Internal Diseases.
Dr. Haserick.
Penetrating Peptic Ulcer.
Dr. Haubrich.
Electrolyte Problems.
Dr. Whitehouse.

P.M. Session
Chairman: Dr. Durham.

2:00 The Carcinoid Syndrome.
Dr. Rupe.
Discussion.

2:25 Unusual Manifestations of Multiple Myeloma.
Dr. Nixon.
Discussion.

2:50 Migraine Equivalents.
Dr. Proctor.
Discussion.

3:15 Intermission.

3:25 Hemachromatosis.
Dr. Abraham.
Discussion.

3:50 Some Unusual Medical Syndromes.
Dr. Durham.
Discussion.

4:15 Clinical Pathologic Conference.
Drs. Robinson and Horn.

Friday, January 29

A.M. Session
Chairman: Dr. Dickson.

9:00 Syndromes of Renal Tubular Dysfunction.
Dr. Frame.
Discussion.

9:25 Management of Acute Renal Failure.
Dr. Morita.
Discussion.

10:00 Kidney Function in Gout.
Dr. Talbott.
Discussion.

10:35 Intermission.

10:45 Panel: Management of Gout.
Drs. Ensign, Talbott, Sigler and Wilson.

11:40 Panel: Cerebrovascular Insufficiency—Diagnosis and Therapy.
Drs. Proctor, Noshay, Darnley, Knighton and Dien.

12:30 Luncheon.

P.M. Session.
Chairman: Dr. Szokolay.

1:30 Hypoventilation States — Detection, Physiologic Features and Management.
Dr. Brinkman.
Discussion.

1:55 Clinical and Physiologic Aspects of Hypercapnia in Chronic Pulmonary Disease.
Dr. Coates.
Discussion.

2:20 Panel: Clinical, Physiologic and Radiologic Characterization of Diffuse Pulmonary Disease.
Drs. Coates, Brinkman and Eyler.

3:00 Panel: The Thyroid Nodule.
Drs. McColl, Block, Miller and Horn.

ABSTRACTS OF RECENT PUBLICATIONS OF THE PROFESSIONAL STAFF OF THE HENRY FORD HOSPITAL AND THE EDSEL B. FORD INSTITUTE FOR MEDICAL RESEARCH

TREATMENT OF ADVANCED BREAST CANCER WITH FLUOXYMESTERONE (HALOTESTIN). V. L. BECKETT, and M. J. BRENNAN. Surg., Gynec. & Obst. 109:235, 1959.

This report concerns our experience with 23 cases of carcinoma of the breast with metastasis, treated with the oral androgen 9 alpha-fluoro-11 beta-hydroxy-17 alphamenthyltestosterone or fluoxymesterone (halotestin). This new oral androgen has been found to be effective in suppressing advanced mammary cancer in postmenopausal patients. Remission occurred in 7 (30 per cent) of our 23 patients—in 2, after hypophysectomy. Fluoxymesterone appears to be less masculinizing than injectable androgens in therapeutic doses. It can cause liver dysfunction such as seen with methyltestosterone.

*BUILD-UP AND REGRESSION OF INHIBITORY EFFECTS OF CHOLIC ACID ON IN VIVO LIVER CHOLESTEROL SYNTHESIS. W. T. BEHER and G. D. BAKER. Proc. Soc. Exper. Biol. & Med. 101:214, 1959.

A study of sequence of events during initiation and regression of inhibition of cholesterol synthesis by dietary cholic acid was made in rats. In the initiation study, increases of liver cholesterol and serum bile acid levels paralleled decreases of liver cholesterol-x-C^{14} activity. There was a decrease in liver phospholipid during the same time interval. In the regression study, serum bile acid and liver cholesterol returned to control levels more rapidly than the rate of liver cholesterol synthesis. The results suggest that dietary cholic acid initially elevates liver cholesterol, which in turn leads to the inhibition of acetate-1-C^{14} incorporation into liver cholesterol.

PLACE OF RADICAL NECK SURGERY IN THYROID CARCINOMA. M. A. BLOCK, J. M. MILLER, and B. E. BRUSH. A. M. A. Arch. Surg. 78:706, 1959.

A radical neck dissection should be carried out for patients with operable carcinoma of the thyroid and evidence of metastases to cervical nodes. Approximately 30% of patients with thyroid carcinoma without palpable cervical lymphadenopathy were found to have metastatic carcinoma to the cervical nodes removed by neck dissections at the time of thyroid surgery or at a later date. Evidence of metastases to cervical nodes will appear later in at least 10% of patients with thyroid carcinoma without palpable cervical lymphadenopathy. A modified neck dissection appears to be justified for many patients with carcinoma of the thyroid in the absence of palpable cervical lymphadenopathy. Although the data do not dictate the absolute necessity for this procedure, better results are suggested if it is done. Complete local eradication of thyroid carcinoma is the most important component of the surgical treatment of this disease. This consists of total lobectomy as the minimal procedure, and frequently total thyroidectomy. Long-term experience with thyroid carcinoma indicates the advisability of a more radical surgical approach in the early stages of the disease. This is in accordance with basic concepts of the surgical therapy of malignancy.

*From Edsel B. Ford Institute for Medical Research.

MANAGEMENT OF THE SWOLLEN ARM FOLLOWING MASTECTOMY. B. E. BRUSH, J. H. WYLIE, J. BENINSON, M. A. BLOCK, and T. J. HELDT. J. Michigan M. Soc. 58:216, 1959.

Edema of the arm may be successfully treated by means of an appliance to reduce the swelling plus the use of a custom-fitted sleeve when the pump is not in use or no longer needed. The pain, discomfort, and swelling are relieved. The incidence of chills, fever, and localized infection is greatly diminished. Strict adherence to instructions is important and medical supervision of the device is imperative. Swollen arm, a troublesome sequela of radical breast surgery, need not be tolerated.

SUBCORNEAL PUSTULAR DERMATOSIS. R. E. BURNS and G. FINE. A. M. A. Arch. Dermat. 80:72, 1959.

Two cases, presenting pustular lesions clinically and histologically similar to the recently described subcorneal pustular dermatosis, are presented. Although there may be a superficial clinical or histologic similarity between it and other bullous and pustular erputions, we feel histologic examination justifies its separation from the previously described pustular and bullous eruptions.

TREATMENT OF MACRODACTYLISM: A CASE REPORT. R. H. CLIFFORD. Plast. & Reconstruct. Surg. 23:245, 1959.

This is a case report of a child with single macrodactyly and treatment which appears to be successful. The plan of operation was to staple the epiphyses of this finger. Very small staples were made by an instrument maker out of stainless steel Kirschner wire. Incisions were made down the lateral side of the finger and all the epiphyseal lines were exposed. Attempts to place these tiny staples across the epiphyseal lines met with failure. The staples were made deliberately small to fit across this area without splitting the articular surface and because they were so small and fragile, it was impossible to drive them into the bone. Since we were unable to staple the epiphysis, it was decided to destroy the epiphysis itself. To do this we used a motorized drill. The drill was inserted directly into the epiphyseal lines and drilled through to the opposite side of the bone. Then, with lateral pressure being applied both on the volar and the dorsal surfaces, the drill cut with its side as does a milling machine, and a slot was cut out of the bone destroying the epiphysis except for a small bony bridge at the dorsal and volar extremities of the slot. The wound was closed in the usual manner and the operative site healed without complications. In the following 3 years it was found that the deformed and treated finger had gained nothing in length, remaining at the 88 mm. originally measured.

COMPARATIVE STUDIES OF OLEANDOMYCIN, TRIACETYLOLEANDOMYCIN, AND ERYTHROMYCIN, WITH A BRIEF REVIEW OF THE LITERATURE CONCERNING OLEANDOMYCIN. J. M. COLVILLE, F. COX, JR., E. L. QUINN. Antibiotics Annual 1958-59, p. 401.

The purpose of this report is to review briefly the literature concerning oleandomycin and triacetyloleandomycin; to present certain laboratory data comparing erythromycin with oleandomycin and triacetyloleandomycin, with particular reference to the in vitro antibacterial activity of these agents; and, finally, in view of these data, to attempt to evaluate the place of triacetyloleandomycin in the treatment of staphyloc-

occal infections. The first part of the present study indicated that within our own geographical area, the large majority of staphylococci isolated from patients with active staphyolococcal infections were sensitive to both eyrthromycin and oleandomycin. The majority of these sensitive strains were eightfold more sensitive to erythromycin than to oleandomycin. The second part of the present study consisted of a comparison of triacetyloleandomycin and erythromycin, with reference to serum concentrations, serum antimicrobial activity, 24 hour urinary excretion, and urinary antimicrobial activity by means of crossover studies in healthy adult volunteers. Comparison of serum concentrations following triacetyloleandomycin with published figures of concentrations after a similar dose of oleandomycin base, indicated that the triacetyl salt produced considerably greater concentrations. The comparative study of erythromycin and triacetyloleandomycin indicated that triacetyloleandomycin produced higher serum antibiotic concentrations throughout the experimental period than did erythromycin. However, serum antibacterial activity studies indicated that despite the previously observed superior serum concentration of triacetyloleandomycin, the antibacterial activity of serum after ingestion of this agent was slightly less than that observed after a similar dose of erythromycin. Third, despite its ability to produce higher serum concentrations, triacetyloleandomycin induces serum antibacterial activity which is somewhat less than that produced by an equal does of erythromycin. On this basis, it would appear that in staphylococcal infections due to organisms sensitive to both antibiotics, erythromycin is the agent of choice.

NEGLECTED HEARING IN CHILDREN. J. L. DILL. JOURNAL-LANCET, 79:357, 1959.

Impaired hearing may be noted at any age. There are two types of hearing loss —the nerve, or perceptive type, and the conductive type. The former may be congenital or acquired. The nerve type of hearing loss cannot be improved. Special education and amplification as indicated should begin at an early age. The conductive type of hearing plification as indicated should begin at an early age. The conductive type of hearing loss is preventable and should respond to therapy. In the small child, we must differentiate among impaired hearing, mental retardation, language disturbance as a result of a mild brain injury, and psychologic factors. Audiometric tests may be given successfully at 3 years of age; others may be given earlier. The majority of children with a moderate hearing loss can be fitted with hearing aids. In children with a nerve type of deafness, hearing aids should be advised by a competent otologist or audiologist. Practically all children handicapped by a hearing loss can be helped either by medication, surgery, or educational means or by any combination of these measures. The results should be as good as the otologist. His careful examination and tests, his accurate diagnosis, and his therapy should produce satisfactory results.

TUMORS OF THE GLOMUS JUGULARIS; REPORT OF NINE CASES, J. L. DILL. Laryngoscpe 69:248, 1959.

A report is made of nine cases of benign tumor arising from the glomus jugulare. The majority (eight) of these tumors were slow growing; however, one patient with cerebellar symptoms had an apparent rapid onset, and a rapid downhill course. The symptoms produced by these tumors depend on the site of origin and their extension. In six patients, the tumor appeared to have its origin in the middle ear;

two had neurological and aural symptoms develop at approximately the same time, and one patient developed aural symptoms, followed a few years later with neurological symptoms. The age of onset (judged from the history) varied from 18 years of age to 51 years of age. Six patients were female, three were males, a ratio of two females to one male. Five of our patients were white, four were colored. Five patients with symptoms and tumors limited to the middle ear, who received either surgery, X-ray, or a combination of both, are alive with no evidence of recurrence of their tumor. X-ray therapy appeared to be beneficial in our patients but has not eradicated the tumor. Bleeding has not been a serious complication except in two cases. At surgery, removal of a rather extensive growth was attempted and produced excessive bleeding with inability to remove the growth entirely in these two patients. Of nine patients with a tumor of the glomus jugulare, six are alive and well with no evidence of recurrence of their tumor. One patient is alive (has had four pregnancies since onset of her tumor) with no local evidence of recurrence, but there is a suspicion of intracranial extension. One patient died of cerebellar extension. One patient is presumed dead.

BRACHIAL PLEXUS BLOCK FOR HAND SURGERY; EXPERIENCE AT HENRY FORD HOSPITAL—600 CASES. J. W. DITZLER, AND R. H. CLIFFORD, J. Occup. Med. 1:363, 1959.

Careful evaluation of 526 brachial plexus blocks for hand surgery indicated 85% to have been completely satisfactory: less than 1% had pneumothorax. Patient acceptability and anesthetic induction time were not problems. Actual complications were significantly few, but those which did occur were either perplexing as to etiology or distressingly difficult to manage. Subsequent to this study, 130 additional brachial blocks were performed, the criteria for selection being essentially the traumatic industrial admission. This has resulted in far less "alleged" complications. It can be said, therefore, that we have somewhat changed our opinion as to the appropriateness of brachial plexus block for hand surgery; we now consider it the best anesthetic for the emergency admissions, who have usually been unprepared for anesthesia and in whom general anesthesia creates a distinct but often overlooked hazard. This is also true of geriatric patients as well as patients suffering from various disease states, particularly those who are on drug therapy which might produce complications, i.e., cortisone, insulin, rauwolfia, and others. From this survey, we now feel that brachial plexus block anesthesia is reasonably safe and usually efficient, but for the young healthy adult in whom elective surgery of the hand is to be performed the institution of an anesthetic method which in our hands is only 75% to 85% successful on the first administration is not ideal. Ideally, this procedure should be reserved for patients in whom general anesthesia is definitely contraindicated, i.e., patients who have recently eaten, geriatric and debilitated patients, or persons on drug therapy which might be interrupted by or in which general anesthesia is a hazard.

SHOULD SPINAL ANESTHESIA BE USED IN SURGERY FOR HERNIATED INTERVERTEBRAL DISK? J. W. DITZLER, P. R. DUMKE, J. J. HARRINGTON, and J. D. FOX. Anesth. & Analg. 38:118, 1959.

Follow-up studies were made on 1062 patients who underwent a total of 766 operations under spinal anesthesia and 333 operations under general anesthesia for

herniated intervertebral disk. Thirty operations with spinal anesthesia and seven with general anesthesia were repeated operations. Follow-up study has not been less than 2 months in any case, and in most the study covered several years. Seven of the patients who had general anesthesia had adhesive arachnitis at the first operation; the condition progressed to paraplegia in two of them. Three patients who had no pathologic condition at the time of the first operation, had adhesive arachnitis at the time of the second operation. Two others had cauda equina syndrome at the time of the second operation. We wish to emphasize that in each of these patients general anesthesia was used. Cauda equina syndrome, which resulted from Nupercaine and cold sterilized ampules in 1937, developed in one patient who had had spinal anesthesia. Spinal anesthesia given to 10 patients with adhesive arachnoiditis had no adverse effects and, in fact, six of the 10 showed remarkable improvement. Spinal anesthesia is an acceptable method when strict adherence to techniques is exercised. It may be used for surgical treatment of herniated intervertebral disk whenever the anesthetic and surgical requirements indicate that the use of a regional technique is desirable. In our experience, no residual neurologic deficits attributable to spinal anesthesia with Spinocaine or Pontocaine occurred.

LEIOMYOSARCOMA OF THE UTERUS WITH UNUSUAL METASTASES. E. T. DRAKE and G. D. DOBBEN, J. A. M. A. 170:1294, 1959.

It appears possible that recurrence of leiomyosarcoma may develop many years after presumably complete excision of the primary tumor. In this patient, metastases became symptomatic 18 years after total hysterectomy. It is the fifth case reported in the literature of metastases in a long bone and the second with retro-orbital metastases. One kidney was also extensively involved.

SIMPLIFIED METHOD OF TREATMENT PLANNING. L. A. DUSAULT. Radiology 73:85, 1959.

Composite isodose curves for a combination of fields give the most complete information about dose distribution. The length of time consumed in constructing such curves for each plan to be considered in treatment of a patient is, however, prohibitive. Precalculated plans can be made up which can be tested in a minimum of time for applicability to a given patient by laying them over his contour tracing. These are simple to construct, and their accuracy is satisfactory. Residents using them soon acquire an understanding of the effect of field arrangement on dose distribution. Details of the construction of isodose curves are given with several samples of such curves.

IMPORTANCE OF THE LATERAL VIEW IN THE EVALUATION OF LEFT VENTRICULAR ENLARGEMENT IN RHEUMATIC HEART DISEASE. W. R. EYLER, D. L. WAYNE, AND J. R. RHODENBAUGH. Radiology 73:56, 1959.

In patients with rheumatic lesions of the mitral valve, the detection of left ventricular enlargement in the lateral view has been the most reliable single roentgen indication of the presence of mitral insufficiency or of an aortic valve lesion. All four views as well as fluoroscopy should be used. The ratio of the length of the segment of the heart which intersects the left leaf of the diaphragm to the internal diameter of the chest has been determined on a lateral view of the chest. Those cases

with a ratio of 0.42 or less have usually not had enlargement of the left ventricle. In those with a ratio above 0.42 the left ventricle has usually been enlarged. When the left ventricle was enlarged, it has in most cases projected behind the shadow of the inferior vena cava for a distance of 15 mm. or more. Patients with a giant left atrium or deformity of the left hemidiaphragm cannot be evaluated by this method. All roentgen signs must be combined; when the roentgen information agrees with the clinical, further study such as left heart catheterization is not required.

STAINING OF FRESH, UNDECALCIFIED, THIN BONE SECTIONS. H. M. FROST. Stain Technol. 34:135, 1959.

Fresh, undecalcified bone sections can be reproducibly and reliably stained by any of the following procedures: (A) Basic fuchsin, 1% in 30% alcohol, 48 hr, 22°C. (B) $AgNO_3$, 0.033 *M*, 48 hr, 22°C.; washing 48 hr in a large volume of distilled water; exposure to light to develop the color. (C) Metallic sulfides (Co^{++}, Pb^{++}, Hg^{++}, Cu^{++}): the nitrate of the metal, 0.033 *M*, 48 hr, 22°C; then Na_2S, 0.033 *M*, 48 hr, 22°C. (D) Alizarin Red S, 0.1% solution in distilled water, 48 hr, 22°C; differentiated 48 hr at 22°C in weakly alkaline water, pH about 8. (E) $KMnO_4$: boiling 8-10 min. in a 0.1 *N* solution. With the exception of D the surface stain must be ground off the section for microscopic examination of its interior. Stain concentration, time and temperature can be altered to suit specific needs.

STOKES-ADAMS ATTACKS COMPLICATING ACUTE MYOCARDIAL INFARCTION; THEIR TREATMENT WITH CONTINUOUS INTRAVENOUS INFUSION OF ISOPROPYLNOREPINEPHRINE. H. H. GALE AND H. L. ENFROY. New England J. Med. 260:1229, 1959.

A case of Stokes-Adams syndrome is presented in which the use of a continuous intravenous infusion of isopropylnorepinephrine was successful in overcoming the bouts of asystole that we had been unable to prevent with either oral administration or subcutaneous, intramuscular or intermittent intravenous injections of the drug.

METAPHYSEAL CHONDRODYSPLASIA OF JANSEN. P. B. GRAM, J. L. FLEMING, B. FRAME AND G. FINE. J. Bone & Joint Surg. 41-A:951, 1959.

A case is described for which the name metaphyseal chondrodysplasia of Jansen is suggested. Biochemical changes were found simulating those caused by hyperparathyroidism, but different and distinctive roentgenographic findings were also evident. Parathyroid exploration was negative for hyperplasia or adenoma. It is postulated that the metabolic changes — hypercalcaemia and hypophosphataemia — may have been secondary to the underlying bone defect.

ANTIBIOTIC CONCENTRATIONS IN DISCS USED FOR SUSCEPTIBILITY TESTING OF STAPHYLOCOCCI. J. E. GREER, R. R. MENARD AND P. F. LESNEY. Antibiotics Annual 1958-59, p. 818.

The distribution of minimum inhibitory concentrations among susceptible and resistant strains of *Staphylococcus aureus* tested by both broth dilution and disc (agar diffusion) techniques with eight antibiotics is reported. These data show these values to be mostly at either extreme, susceptible or resistant. Thus, two discs are sufficient to classify staphylococci as susceptible, moderately resistant, or resistant,

since few intermediates occur. One disc is sufficient if concentrations and zone sizes are properly standardized. Some reasons for inaccurate discs are discussed.

*STUDIES ON SUCCINIC DEHYDROGENASE. X. REACTIVITY WITH ELECTRON CARRIERS IN RESPIRATORY CHAIN PREPARATIONS FROM HEART. XI. INACTIVATION BY CYANIDE AND ITS MECHANISM. A. GIUDITTA AND T. P. SINGER. J. Biol. Chem. 234:662, 1959.

The characteristics and mechanism of action of the cyanide inactivation of succinic dehydrogenase activity in particulate preparations have been investigated. The soluble enzyme isolated from heart is insensitive to cyanide regardless of the method of assay. Particulate preparations are inactivated by incubation with cyanide to the following maximal extent: oxidation of succinate by cytochrome *c*, methylene blue, brilliant cresyl blue, and dichlorophenolindophenol, 100 per cent; succinate-ferricyanide reaction, 65 to 70 per cent; succinate-phenazine methosulfate reaction, 50 per cent; fumarate-leucomethyl viologen reaction, 50 percent; fumarate-reduced riboflavin 5-phosphate reaction, 0. In confirmation of the results of Tsou it was found that the inactivation by cyanide progresses as a reaction of first order, of which the rate depends on temperature and cyanide concentration. Contrary to Tsou's report, the rate was found to vary markedly with pH, and the pH-dependence is not the same in the inactivation of the succinate-methylene blue and succinate-phenazine methosulfate assays. The inactivation is characterized by two distinct effects: loss of activity at infinite concentration of electron carrier (V_{max}) and loss of affinity for electron carriers. Both of these effects are prevented by compounds which reduce succinic dehydrogenase (succinate, hydrosulfite, reduced diphosphopyridine nucleotide) but only the second effect is reversed by reducing agents. Although reduced diphosphopyridine nucleotide prevents the action of cyanide on succinic dehydrogenase, cyanide does not abolish the oxidation of reduced diphosphopyridine nucleotide in heart muscle preparations. The cyanide inactivation described has been encountered only in heart preparations; it is not observed in brain or yeast. The possible mechanism of the cyanide inactivation and its implications on the organization of the respiratory chain in sarcosomes have been discussed.

IRIDENCLEISIS; TECHNIQUE AND RESULTS IN NINETY-FIVE CONSECUTIVE OPERATIONS. M. W. HAISTEN AND J. S. GUYTON. A.M.A. Arch. Ophth. 61:727, 1959.

The operative technique employed, the results obtained, and the complications encountered in 95 consecutive iridencleisis over a three-and-one-half-year period are presented. A successful result was obtained in 84% of the cases (acute congestive, chronic open-angle, and chronic narrow-angle glaucoma). We believe iridencleisis is the operation of choice in those cases of acute congestive glaucoma in which permanent embarrassment of the outflow mechanism has occurred. It would appear that iridencleisis and cyclodialysis are of comparable effectiveness for chronic primary noncongestive glaucoma of either the open- or narrow-angle type (with the exception of those cases occurring in the Negro race, in which we would prefer cyclodialysis). We do not feel that iridencleisis is indicated in aphakic or other secondary glaucomas.

*From Edsel B. Ford Institute for Medical Research.

METHODS OF FIXATION IN MANDIBULAR BONE GRAFTS. F. A. HENNY AND W. D. MCCLELLAND, JR. J. Oral Surg., Anes. & Hosp. Dent. Serv. 17:34, 1959.

A new appliance is described which can be used quickly, easily and effectively to retain mandibular segments in their correct anatomic relationships after partial resection of the mandible. The device consists of a Kirschner stainless steel pin, 9 inches long and 3/32 inch in diameter, threaded for its entire length. Two nuts and washers are provided with each pin. Both insertion and removal are rapid and simple.

SUBTOTAL RECONSTRUCTION OF THE THUMB; TUBED-PEDICLE FLAPS WITH TACTILE RESTORATION. A. P. KELLY, JR. A.M.A. Arch. Surg. 78:582, 1959.

The tubed-pedicle flap and bone graft can effect a satisfactory restoration of the amputated thumb. This method can be utilized for a loss through the proximal phalanx or metacarpal. I feel, however, that it is most suitable for losses through the metacarpophalangeal joint or proximal phalanx. I believe that the major disadvantage of the tubed-pedicle flap, its lack of stereognosis, can be combated by the neurovascular pedicle flap or the proximally based palmar flap. Two illustrative cases are presented.

CHLOROTHIAZIDE AND HYDROCHLOROTHIAZIDE IN THE TREATMENT OF CONGESTIVE HEART FAILURE. J. W. KEYES, G. M. BRENEMAN, AND H. ALVAREZ, JR. Internat. Rec. Med. 172:454, 1959.

In the past two years, a new class of potent oral diuretic agents, derived from the aromatic sulfonamides and belonging to a group known as benzothiadiazines, has been introduced to the medical profession. The first major breakthrough in producing a nontoxic and highly active oral diuretic resulted in the development of chlorothiazide, 6-chloro, 7-sulfamyl, 1, 2, 4-benzothiadiazine-1, 1-dioxide. Since then, a second and more powerful derivative, hydrochlorothiazide, has been synthesized; it is designated as 6-chloro-7-sulfamyl-3, 4-dihydro-1, 2, 4-benzothiadiazine-1, 1-dioxide. Both of these compounds are very active saluretic agents, causing the excretion of large amounts of sodium, chloride, and, to a lesser extent, potassium. It is to this activity that the drugs owe their effectiveness in the management of edema states, particularly congestive heart failure. Hydrochlorothiazide differs from chlorothiazide in having no double bond in the heterocyclic ring and appears to be several times more effective in its diuretic activity mg. for mg., as will be shown later. Chlorothiazide and hydrochlorothiazide were administered to separate series of patients with congestive failure. Both drugs were potent oral diuretic agents for the short- and long-term management of these patients. One of these drugs (hydrochlorothiazide) was also effective by intravenous administration. Dosage and toxicity of the two drugs are discussed.

RECENT DEVELOPMENTS IN CARDIAC SURGERY. C. R. LAM. Chicago M. Soc. Bull. 62:68, 1959.

There is so much change and expansion in the field of surgery of the heart it is interesting to prepare a report on recent developments. It is common knowledge

that the most dramatic advances have been made because of the break-through into open heart technics by Lillehei and the group at the University of Minnesota. It is now almost five years since their first successful by-pass of the heart and lungs by means of cross circulation with a human donor. Within a year, they were able to eliminate the donor by utilizing a bubble type of oxygenator and open heart surgery took its place in surgical practice. Also, the test of time has been applied to some of the earlier cardiac operations so that we now know if they have shortcomings and of their "durability." The surgical management of the following conditions is discussed, patent ductus arteriosus, coarctation of the aorta, mitral stenosis and insufficiency, aortic stenosis, aortic insufficiency, pulmonic valve stenosis, atrial septal defect, ventricular septal defect, tetralogy of Fallot, and coronary artery insufficiency. In spite of the progress in heart surgery which has been reported, many problems still challenge the investigative surgeon. A successful operation for transposition of the great vessels still has to be devised, and there are other congenital and acquired lesions which demand attention. With continued intense interest, further improvements in the near future are inevitable.

EFFECT OF ANTIBIOTIC THERAPY ON THE EMERGENCE OF RESISTANT STAPHYLOCOCCI IN CUTANEOUS BACTERIAL INFECTIONS. C. S. LIVINGOOD, J. E. GREER, R. E. BURNS, AND R. R. MENARD. J. Invest. Dermat. 32:485, 1959.

Our experience regarding the emergence of antibiotic-resistant *Staph. aureus* in skin lesions of patients with cutaneous bacterial infections, following therapeutic trials with tetracycline ointment, erythromycin ointment, neomycin ointment (or lotion), bacitracin ointment, or neomycin-bacitracin ointment, or after oral administration of tetracycline, erythromycin, or novobiocin is reported. A total of 354 patients met the following criteria for inclusion in this study: 1) Presence of an apparent clinical primary or secondary cutaneous bacterial infection. 2) Isolation from involved sites, before therapy, of *Staph. aureus* susceptible to the antibiotic which was administered systemically or applied topically. 3) Availability of follow-up cultures after varying periods of time following the antibiotic therapy. There was a change from a sensitive to a resistant antibiogram in 16 of 136 patients treated with either tetracycline or erythromycin ointment. Of the 109 patients treated topically with either neomycin, bacitracin, or the combination of neomycin-bacitracin, there was either no change in the antibiogram or *Staph. aureus* was not isolated following treatment. Emergence of antibiotic-resistant *Staph. aureus* was noted in 17 of 92 patients with skin infections, treated systemically with tetracycline, erythromycin or novobiocin. The problem of emergence of antibiotic resistant *Staph. aureus* following the use of topical and systemic antibiotic therapy for the treatment of cutaneous bacterial infections is of greater significance in in-patients than in out-patients. Our present policy regarding the use of systemic and topical antibiotic therapy for the treatment of bacterial infections of the skin is summarized.

ALTERED PROGNOSIS WITH CARDIAC MASSAGE; CARDIAC RESUSCITATION IN ACUTE MYOCARDIAL INFARCTION — REPORT OF TWO SUCCESSFULLY TREATED CASES. S. N. NICKEL AND H. H. GALE. J.A.M.A. 170:23, 1959.

In two instances patients with previous symptoms of myocardial infarction

collapsed suddenly and became pulseless. Artificial respiration was given by insufflation, and immediate thoracotomy was performed to permit rhythmical compression of the heart, which was in a state of asystole. Intracardiac injection of 0.5 cc. of 1:1,000 aqueous solution of epinephrine was followed by ventricular fibrillation. Normal cardiac rhythm was restored by use of an electrical defibrillator in each case, and both patients survived without signs of injury to the brain. This is in accord with other published data indicating that these methods of resuscitation, if applied without delay, greatly improve the prognosis of patients with acute myocardial infarction.

LIPOID NODULES IN CHRONIC RHEUMATOID ARTHRITIS; NODULOS LIPOIDE IN CHRONIC ARTHRITIS RHEUMATOIDE. R. K. Nixon, Jr., and R. H. Durham. Arthritis & Rheumat. 2:27, 1959.

A case of advanced rheumatoid arthritis with multiple lipoid nodules is presented. No conclusions as to the particular significance of lipoid nodules are attempted, but their recognition as an unusual feature associated with chronic rheumatoid is stressed. The origin of lipoid nodules from ordinary rheumatoid nodules is reviewed. They are concluded to be probably identical to so-called calcium cysts previously reported in rheumatoid patients with vitamin D intoxication. The etiologic role of vitamin D, however, is questioned.

BLEEDING, PLATELETS, AND MACROGLOBULINEMIA. M. R. Pachter, S. A. Johnson, T. R. Neblett, and J. P. Truant. Am. J. Clin. Path. 31:467, 1959.

Two cases of primary macroglobulinemia of Waldenström were exhaustively evaluated from the standpoint of modern methods on coagulation. The literature regarding the hemorrhagic diathesis is reviewed and evaluated. A coating of the platelets by macroglobulins as a cause of bleeding in macroglobulinemia of Waldenström is hypothesized and substantiated on the basis of coagulation, immunochemical, and electron and fluorescent microscopic studies. A potential deleterious effect of macroglobulins on erythrocytes and leukocytes is indicated. The relation between the macroglobulin and cellular surface is discussed.

ACUTE APPENDICITIS; AN ANALYSIS OF COMPLICATIONS IN 551 PATIENTS. J. L. Ponka, H. L. Shields, and D. M. Evans. J. Michigan M. Soc. 58:415, 1959.

The fact that early appendectomy has long been established as the curative procedure for acute appendicitis needs emphasis. Antibiotics are not effective in the treatment of appendicitis associated with appendicular obstruction. Complications of appendicitis are much too common, (16.46 per cent in this series) and are the result of delays in diagnosis and surgical treatment. Antibiotics, surgical drainage, gastro-intestinal tract decompression and blood transfusions are life saving adjuncts in the treatment of complications. The public and the profession as well need to be reminded that appendicitis can be disabling, as well as fatal, if neglected.

PERIODONTICS FOR THE GENERAL PRACTITIONER. Z. A. Reader. J. Michigan Dent. Assoc. 40:179, 1958.

Most patients that have had extensive periodontal treatment should return

approximately every three or four months for thorough oral prophylaxis and for examination of gingival health, pocket depth, tooth mobility, etc. If necessary, returning periodontal problems can be treated and the occlusion readjusted. Complete dental films should be taken annually. The patient must never be told that his case has been cured but rather he should be told that the case is controlled and it will only remain controlled in the future through his cooperation by proper home care and periodic examination and treatment by the dentist. Because periodontal diseases are so universal the general practitioner must recognize and treat them. The cases which are too involved may be referred to a periodontist. After the periodontal work is finished the periodontist may make suggestions to the referring dentist for mouth rehabilitation. The general practitioner should be especially interested in the prevention of periodontal disease with the same zeal which he has had in the prevention of dental caries. This can be accomplished only by patient education and immediate treatment of incipient periodontal alterations.

*STUDIES ON CHOLINE DEHYDROGENASE. I. EXTRACTION IN SOLUBLE FORM, ASSAY, AND SOME PROPERTIES OF THE ENZYME. G. RENDINA AND T. P. SINGER. J. Biol. Chem. 234:1605, 1959.

The assay of choline dehydrogenase activity in mitochondrial as well as soluble preparations with phenazine methosulfate as acceptor has been described. Electron acceptors employed in the past for the assay of this enzyme (cytochrome *c*, ferricyanide, methylene blue, and 2, 6-dichlorophenolindophenol) either do not react directly with the dehydrogenase and consequently measure a variable part of its activity, or they are unreliable because of the extensive dependence of the measured activity on dye concentration. Choline dehydrogenase has been brought into solution in good yield by a mild procedure involving treatment of mitochondria or acetone powders thereof with certain snake venoms. Evidence has been presented that the active component in liberating the dehydrogenase in soluble form is phospholipase A. The process appears to depend on the point of attack and on the structural specificity of the particular phospholipase, since plant phospholipase D and the phospholipase A of certain venoms are inactive, whereas the phospholipase A of other venoms is active in dissolving the dehydrogenase. Upon treatment with phospholipase A the reactions of the dehydrogenase with cytochrome *c* and ferricyanide are abolished, probably as a result of the uncoupling of the enzyme from the factors linking it to these acceptors in respiratory chain preparations. The enzyme extracted by this means does not sediment at 144,000 $\times$ *g* for 1 hour and does not precipitate on repeated freezing and thawing or on prolonged dialysis. Contrary to claims in the literature, choline dehydrogenase is not stimulated by flavin adenine dinucleotide or diphosphopyridine nucleotide, even after extensive dialysis, in either soluble or mitchondrial preparations. The apparent stimulation of the dehydrogenase by added diphosphopyridine nucleotide in assays involving the respiratory chain (choline oxidase) has been explained as an indirect effect involving the activation of betaine aldehyde dehydrogenase, with consequently increased rate of O_2 uptake and removal of the aldehyde which is inhibitory to choline dehydrogenase. Some properties of the soluble dehydrogenase have been described.

*From Edsel B. Ford Institute for Medical Research.

MALABSORPTION SYNDROME AND DIARRHEA; A PANEL DISCUSSION. D. J. SANDWEISS, D. ADLERSBERG, A. B. FRENCH, R. H. MARSHAK, H. L. BOCKUS, AND R. J. PRIEST. J. Michigan M. Soc. 59:772, 1959.

THERAPY OF PRIMARY MALABSORPTION. ROBERT J. PRIEST.

Although clinical and symptomatic improvement has been observed in this recent series of patients, the period of observation has been of too short duration to permit conclusions. Sprue has been a disease renowned for its chronic remitting course. Spontaneous remissions are not infrequent. The importance of the psychological effect of a new management regime must be evaluated. In fact, an important measure in the management of primary malabsorption is attention to the factors of nervous stress and fatigue. We have seen one patient who did not secure any symptomatic relief from the gluten-free diet during a period of time when she had problems in the family situation. Six months later, after resolution of the situational factors, and an opportunity for an extended vacation, she responded promptly when the gluten-free diet was again attempted. Many patients should be encouraged to take short periods of rest during the day and to avoid nervous or physical fatigue. Therapy of primary malabsorption must be directed towards improving the patient's nutrition and correction of the deficiency states. No single drug nor dietary program can be given complete reliance. The gluten-free diet offers promise of a valuable adjunct to the previous dietary management. The corticosteroids are an important adjunct in the control of patients who have not responded to therapy with vitamin and mineral supplements.

LOCALIZATION OF ACETYLCHOLINESTERASE IN THE COCHLEA. H. F. SCHUKNECHT, J. A. CHURCHILL, AND R. DORAN. A.M.A. Arch. Otolaryng. 69:549, 1959.

We have previously published the results of studies showing that acetylcholinesterase is present along nerve fibers and in dense accumulations at the bases of the hair cells in the organ of Corti of the cat. In the present study fresh cat cochleas were perfused with acetylthiocholine in the presence of cupric ions, the solutions passing from the round window through the helicotrema and out the oval window. The cochleas were fixed, decalcified, sectioned, and counterstained. The copper sulfide deposits resulting from activity of acetylcholinesterase were found to be markedly decreased in six cochleas in which the olivocochlear bundle had been successfully sectioned in the medulla. Acetylcholinesterase was not decreased in any of the control ears or in the two ears in which the olivocochlear bundle had not degenerated after unsuccessful section. The esterase remained in the neighborhood of hair cells that had been destroyed by streptomycin in three cats. It was concluded that the presence of acetylcholinesterase in the cochlea was dependent upon the integrity of the olivocochlear bundle. The evidence revealed that fibers of the olivocochlear bundle terminate upon or very close to the cochlear hair cells, and that these fibers are cholinergic. Acetylcholine liberated at the endings of the olivocochlear tract fibers may alter the excitability state of the hair cells or the acoustic nerve endings. The amacrine cells of the retina, which are known to contain acetylcholinesterase, may subserve a function similar to that of Rasmussen's bundle in the cochlea. Perhaps other sensory end-organs should be investigated for cholinergic efferent nerve fibers.

TYMPANOPLASTY. H. F. SCHUKENCHT AND S. OLEKSIUK. Laryngoscope 69:614, 1959.

Tympanoplasty surgery is an exercise in micro-surgical technique which requires good judgment, great patience and an understanding of the physiological principles of sound transmission. Success depends upon meticulous removal of diseased tissues and reconstruction of the tympanic space so as to accomplish a columnella effect and/or a pressure differential at the windows. It is most important that the mucosa of the tympanum, medial tympanic wall and round window area be cautiously preserved and that the skin graft, preferably full-thickness from the post-auricular sulcus, be trimmed, fitted and packed into place with great care. Ten per cent of the patients were made worse by 5 db or more, but several of these losses were less than 15 db and have been corrected subsequently by surgical revision. The percentage of good cases increases with time as our surgical technical ability has improved. The two main reasons for tympanoplasty failure are: 1. partial graft necrosis, and 2. scarring of the graft into the hypotympanum. Four of the patients have had a significant unexplained loss of bone conduction thresholds. An analysis of the results of 160 tympanoplasties reveals that a 30 db level was acquired by 82 per cent of Type I cases, 70 per cent of Type II cases, 48 per cent of total plastic cases (Type III-A and IV-A) and 70 per cent of minor plastic cases (Type III-B and IV-B). Our experience has shown that damage to ossicles and tympanic membranes was less in the younger age group and the success of tympanoplasty operation depends in part upon early intervention in chronic irreversible suppurative middle ear disease.

EFFECT OF ANTIBACTERIAL AGENTS ON CLEAN WOUNDS. C. K. SERGEANT, J. L. PONKA, AND B. E. BRUSH. A.M.A. Arch. Surg. 78:480, 1959.

It was found that the antibacterial agents tetracycline (Achromycin), chlortetracycline (Aureomycin), bacitracin, chloramphenicol (Chloromycetin), neomycin, polymyxin B, and oxytetracycline (Terramycin) generally do not retard or accelerate the rate of wound healing, with the exception of chlortetracycline, which was found to retard routinely the time for healing from two to six days.

TRAUMATIC EPIDERMOID CYSTS INVOLVING DIGITAL BONES; EPIDERMOID CYSTS OF THE DISTAL PHALANX. J. C. SIERACKI, AND ALEX P. KELLY, JR. A.M.A. Arch. Surg. 78:597, 1959.

Epidermoid cysts in the digital bones generally follow trauma and represent a distinct clinicopathologic entity. The clinical, roentgenologic, and histologic features allow the correct diagnosis in all cases. Surgical treatment is curative, and will allow preservation of the distal phalanx in the majority of cases. A significant degree of pseudoepitheliomatous hyperplasia in the cyst wall was found in four out of the nine cases presented in this series.

CURRENT PROBLEMS IN PERIPHERAL ARTERIAL SURGERY. R. F. SMITH. Heart Center Bull. 15:1, 1958.

An angiographic survey is essential in evaluating the type of arteriosclerotic occlusive disease present in patients so afflicted and greatly assists the vascular surgeon in choosing those individuals in whom an appropriate angioplastic procedure may be employed with reasonable success. As the disease process has a variety of pathological

manifestations, one must be selective in establishing the indications for an operation and utilize a procedure suitable for the specific circumstances. The guiding principle should be to avoid any surgery that could further embarrass the circulatory status of an extremity. We are currently favoring a long bypass of elastic Dacron for the management of femoro-popliteal occlusions with the hope that a greater degree of late patency will be achieved than with arterial homografts.

PRESENT STATUS OF ARTERIAL SUBSTITUTES. R. F. SMITH AND D. E. SZILAGYI. J. Michigan M. Soc. 58:77, 1959.

As yet no truly ideal arterial substitute has been developed. Further investigation and clinical trial will be necessary before this goal is achieved. Autogenous vein grafts are readily available, especially in emergency circumstances, but are limited as to their dimensions. Experimentally, heterografts have been shown to be completely unreliable. Both venous and arterial homografts, because of their lack of durability, should be limited to the occasional instance where the technical difficulties in the case require their superior ability to remain patent under adverse conditions or in older individuals where the need for long-range function is not great. All the rigid synthetic plastic prostheses suffer from the disadvantage of kinking when bent, making their clinical usefulness quite limited. Elastic nylon tubes satisfactorily overcome the problem of kinking but show progressive deterioration of tensile strength which drastically limits their clinical application. In almost all instances we have found an elastic Dacron prosthesis to function very satisfactorily without loss of tensile strength, and we feel that this is the most suitable type of arterial substitute at the present time.

OSSIFICATION OF REGENERATED MEDIAL SEMILUNAR CARTILAGE. S. S. STANISAVLJEVIC. Acta Orthop. Scandinav. 28:224, 1959.

The first instance of post-traumatic ossification of a regenerated medial meniscus with limitation of flexion of the knee joint was observed. The meniscus was removed and hydrocortisone was injected into the cavity of the joint. The treatment restored the normal use of the leg.

CHLOROTHIAZIDE THERAPY IN OBSTETRICS AND GYNECOLOGY. L. B. STEVENSON, AND C. P. HODGKINSON. Am. J. Obst. & Gynec. 77:1286, 1959.

After appraisal of the reasons for elevation of blood uric acid from the administration of chlorothiazide, it was observed that this occurred in both obstetric and gynecologic patients. Hyperuricemia was not caused by hemoconcentration since uric acid levels rose out of proportion to the other constituents of the blood. The reason for the increase in uric acid concentration is not established by this study and whether this resulted from altered renal excretion of uric acid or dysfunction of metabolism is not known. While the clinical importance of hyperuricemia resulting from chlorothiazide treatment appears to be minimal, its obstetric import lies in the confusion which may result from using serum uric acid levels as aids in diagnosis and prognosis in toxemia. Results of this study suggest that chlorothiazide is a potent diuretic agent that is relatively free of toxicity. The equimolar excretion of sodium

and chloride makes the drug comparatively safe for administration during pregnancy. Although the drug does not cure toxemia of pregnancy, our findings would put chlorothiazide in the group of drugs used as adjunctive in its treatment. These conclusions are similar to those of Finnerty and associates who used chlorothiazide in patients with toxemia of pregnancy.

ANTEROMEDIAL APPROACH TO THE POPLITEAL ARTERY FOR FEMOROPOPLITEAL ARTERIAL GRAFTING. D. E. SZILAGYI, J. G. WHITCOMB, AND R. F. SMITH. A.M.A. Arch. Surg. 78:647, 1959.

An approach is described to the popliteal artery that makes it possible to insert long femoropopliteal bypass implants in an uninterrupted technical sequence. Bridging, in this manner, a longer segment of diseased artery, this operation promises to reduce the late failure rate of grafting operations for occlusive disease of the femoropopliteal area.

HEMODYNAMIC FACTORS IN ARTERIAL GRAFTING: AN EXPERIMENTAL STUDY OF ANASTOMOTIC TYPES, GRAFT SIZE AND GRAFT SURFACE CHARACTERISTICS. D. E. SZILAGYI, J. G. WHITCOMB, P. WAIBEL, AND W. SCHENKER. S. Forum 9:319. 1959.

Measurements of blood volume-flow with the bubble flow-meter in the iliac arteries of the dog have shown that: A properly constructed end-to-end anastomosis is almost as efficient in transmitting blood as the intact artery. An end-to-side anastomosis is less efficient hemodynamically than an end-to-end anastomosis, but its efficiency to a large extent depends on the size of the angle between the component channels. By making the angle small the performance of this type of anastomosis can be made to come very close to that of an end-to-end anastomosis. A graft placed as a bypass is less efficient hemodynamically than a direct replacement of the same size but the difference can be markedly reduced and even eliminated by appropriate surgical technique. An increase in the diameter of a vacsular graft by a factor of up to 2 brings about an increase in blood volume-flow which, however, is not proportional to the dimensional increase. An increase in diameter above a factor of 2 results in a decrease in volume flow. A prosthesis with rough or corrugated (crimped) luminal surface is less efficient than a prosthesis whose wall is uncorrugated and smooth.

PRIMARY ALDOSTERONISM DUE TO ADRENAL HYPERPLASIA; OCCURRENCE IN A BOY AGED 10 YEARS. B. THERIEN, R. C. MELLINGER, J. R. CALDWELL, AND P. J. HOWARD. A.M.A.J. Dis. Child. 98:90, 1959.

The details of a case of primary hyperaldosteronism occurring in a child 10 years of age have been presented. This hyperaldosteronism was proved to be due to bilateral adrenal hyperplasia chiefly involving the zona fasciculata. It is postulated that this hyperplasia was congenital in origin. Hyperaldosteronism should be considered in the differential diagnosis of any case of "essential" hypertension or of unexplained polyuria in children. The determination of serum potassium and urinary pH are useful screening tests in these patients. When hyperaldosteronism is caused by adrenocortical hyperplasia, bilateral total adrenalectomy is recommended. Maintenance of the patient postoperatively with adrenocortical hormones has been completely satisfactory.

GLUCAGON FOR TREATMENT OF INSULIN HYPOGLYCEMIA: ITS USE IN THE PATIENT WITH DIABETES. F. W. WHITEHOUSE, AND H. G. BRYAN. Am. Pract. & Digest Treat. 10:1326, 1959.

Hypoglycemic reactions in the diabetic using insulin are alarming to the patient and the family. In establishing a program of control, hypoglycemic reactions make the course more labile with rebound hyperglycemia from use of glucose to control the reactions. Thus, the substance produced by the alpha cells of the islets of Langerhans, and now available in crystalline form as glucagon, having a hyperglycemic effect, has potential uses in labile diabetics. Though the material is not on the market, the studies detailed here are nevertheless of interest. Glucagon for the relief of insulin hypoglycemia has been used successfully over one hundred times during the past year. Generally it has been given subcutaneously in a dosage of 10 to 40 mcg./Kg. body weight. No toxicity has occurred. Its advantages and disadvantages are discussed.

BOOK REVIEW

ENCYLOPEDIA QF MEDICAL SYNDROMES. BY ROBERT H. DURHAM, M.D. F.A.C.P. Chief Physician, Division of General Medicine, Henry Ford Hospital. New York, Paul B. Hoeber, Inc., 1960.

It has been a privilege to review this fascinating volume which contains such a variety of subjects, including as it does a comprehensive discussion of nearly 1,000 medical syndromes. The collection of this unprecedented number of syndromes is an impressive achievement and obviously required a widespread search of the world literature. Although some of the subject titles are readily recognized and others are vaguely familiar, many are unusual and rare.

The general plan and arrangement of the book are excellent. The various syndromes as well as their eponymic and descriptive synonyms are arranged alphabetically. Conveniently listed with each subject title are associated or interrelated syndromes. As a typical example:

PICKWICKIAN SYNDROME.

Synonyms: Cardiopulmonary-obesity syndrome, reversible obesity-cardio-respiratory syndrome, alveolar hypoventilation-obesity syndrome.

See also *Gelineau's syndrome: Kleine-Levin syndrome; postural syndrome; hypoventilation syndrome.*

The text of the individual syndromes is presented in a well organized editorial style of summarization and includes both the lesser known as well as the better known facts concerning each subject. Pertinent comments are made concerning historical data, genetic relationships, hereditary, congenital and familial factors, the reported incidence and sex ratios. Recorded in sequence are clinical manifestations, laboratory and pathologic findings, differential diagnosis, the clinical course, prognosis and known therapy and therapeutic results. These amassed facts are condensed into a brief but comprehensive summary without any evidence of a stereotyped pattern or repetition of style.

The composite result is a vast amount of factual information concerning a large number of associated clinical patterns or relationships. Many of these syndromes have not before been incorporated into text; at least no similar complete reference source has previously been available.

There is an index arranged by classification under the various body systems. The alphabetization of subject titles provides an adequate cross reference of related syndromes.

Aside from the educational import of this book as a factual reference source, it commands attention for other basic reasons. This reviewer foresees for it two potential significant influences: (1) That it will accelerate a developing trend by means of which syndromes may to an increasing degree supplant diseases as a definitive medical term. During the past decade it has become increasingly evident that the number of new diseases is becoming more limited, although a larger number of medical syndromes is becoming apparent. (2) That both eponymic and descriptive syndromes, hitherto largely omitted in the index of text-books and almost completely ignored in other standard reference indexes, will command more recognition in these index reference sources in the future. This book will undoubtedly be a contributing influence in these two directions.

Aside from being a splendid contribution to medical needs, this volume is timely, and in many respects, timeless. It is without question the most comprehensive and authoritative source pertaining to medical syndromes ever published in the English language. With equal certainly the scope and character of its subject matter will make it an indispensable text for many years to come. As a further attest to the high standard of excellence with which this scholarly compedium is regarded in critical circles, the Foreword is by T. R. Harrison, eminent medical author and teacher.

HENRY FORD HOSPITAL MEDICAL BULLETIN

Published quarterly by the Professional Staff of the
Henry Ford Hospital and The Edsel B. Ford Institute for Medical Research

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